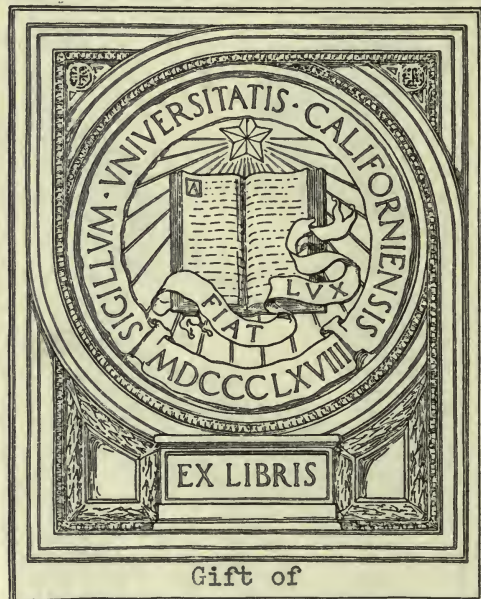


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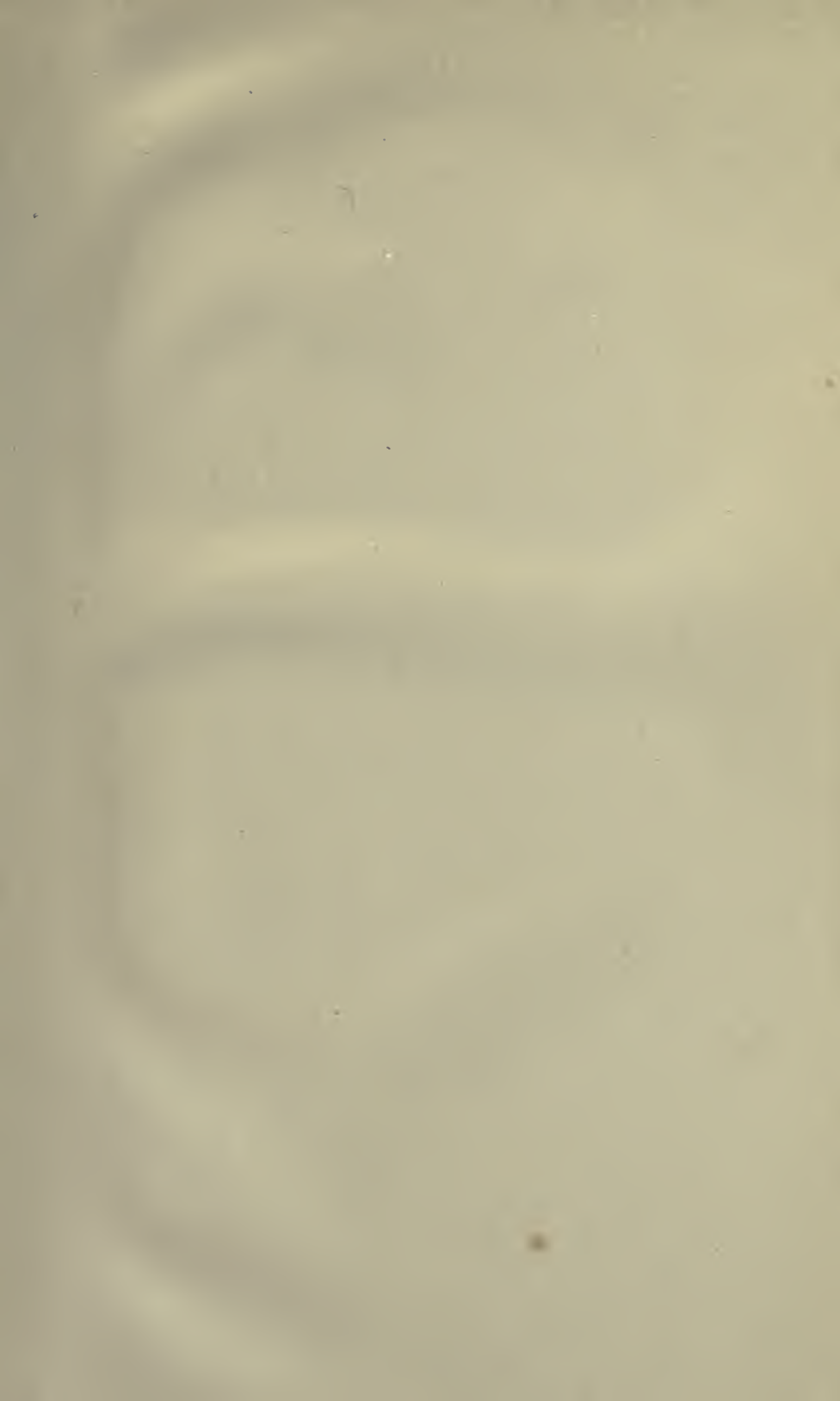


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Fats and Fatty Degeneration

A PHYSICO-CHEMICAL STUDY OF EMULSIONS AND
THE NORMAL AND ABNORMAL DISTRIBUTION
OF FAT IN PROTOPLASM

BY

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AND

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TO

Louella Chapin

TEACHER, COUNSELOR AND INSPIRATION DAILY
TO A THOUSAND YOUTHS

44447

Breath and all in your composition that is igneous naturally ascend, yet, obedient to the order of the whole, they retain their place here in the compound. The earthy and humid parts, on the other hand, naturally descend, yet are raised and retain a position other than their natural one. Thus the elements, wheresoever placed, obey the law of the whole, waiting till the signal be given for their dissolution.

MARCUS AURELIUS.

PREFACE.

THE following pages give in collected and somewhat amplified form the results of experiments which have not previously been published in English, excepting in abstract form in *Science*. While our earlier colloid-chemical studies had compelled a desultory consideration of some of the problems here dealt with, this detailed study of the question of the fat in the cells is less than two years old. We turned to this fat problem in order to escape from older colloid-chemical studies on œdema, nephritis and allied subjects.¹ In this, however, we were early doomed to disappointment. Without intent on our part, the conclusions of these newer studies dovetail with and corroborate the older ones. A house previously looked at from within is here seen from without — but it is the same house.

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UNIVERSITY OF CINCINNATI.

July 20, 1916.

¹ See "œdema and Nephritis," second edition. John Wiley and Sons, Inc., New York, 1915.

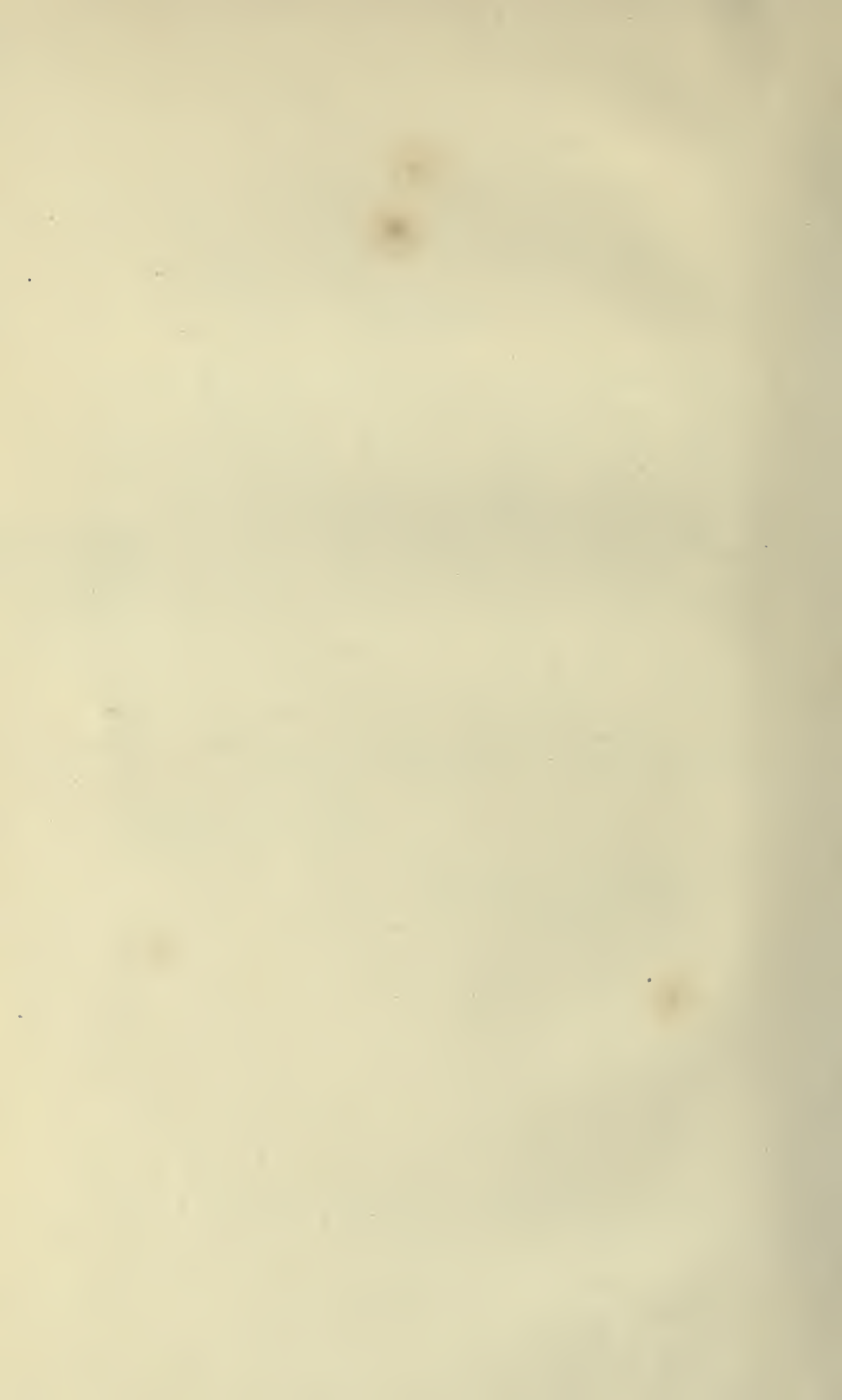


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I. THE ARGUMENT.

FATS AND FATTY DEGENERATION

I. THE ARGUMENT.

I.

THIS introductory chapter follows a plan which, when used in a previous monograph, elicited favorable comment. It is an abstract of the entire volume, designed for those who have not time to read the whole book. The experimental evidence as presented in these first pages is necessarily condensed; where it proves inadequate to carry conviction to the reader, he may follow the extended argument by turning to pages referred to in the course of the abstract.

II.

The importance of the emulsions and of a knowledge of their properties for various problems in physiology, pathology and technology, is emphasized. (See pages 19 to 20.)

An emulsion is by definition a mixture of two immiscible liquids in each other, as of oil in water. Since the one liquid is subdivided (dispersed) in the other, an emulsion is one of the group of the so-called dispersed systems. Since the properties of the one liquid are greatly different from those of the second in an emulsion, we note that it is made up of different phases. An oil-in-water emulsion is, in other words, diphasic. (See page 20.)

To the pure chemist, an emulsion is a mechanical mixture of two or more materials and so to him they are all alike, when once the materials to make up an emulsion and their amounts are settled upon. But this conclusion is wrong. From the same quantities of oil and water, for example, two entirely different types of emulsions may be produced which have totally different properties. There may be made an emulsion of the oil in the water or of the water in the oil (See pages 20 to 21.)

Cottonseed oil and water are chosen as the materials from which to produce emulsions in order to study the laws regarding their production, their maintenance, their destruction and their general properties.

Oil in contact with pure water does not lead spontaneously to the formation of an emulsion. In order to subdivide the one material in the second, mechanical mixers of different types must be used. The construction of these and their relative merits are discussed. (See pages 21 to 25.)

The amount of cottonseed oil that may be permanently emulsified in pure water on beating the two together is very small, not exceeding a fraction of one percent. These emulsions are, however, stable. The oil particles in such emulsions are rather small, their dimensions lying within the realm of the colloids. These low concentrations of oil in water, therefore, really represent colloid suspensions of oil in water and possess not only the stability characteristics of such systems, but also their well known "saturation limit." (See pages 25 to 26.)

The term "emulsion" is ordinarily used to cover the subdivision of one fluid in a second in amounts exceeding these low values. The mixture must, moreover, show a fair degree of stability; in other words, the two liquids constituting the dispersoid must not separate in the course of weeks, months or years. A temporary subdivision of any quantity of oil in a given volume of water, or the converse, can, of course, be obtained by merely beating the two together. The problem of emulsification, therefore, really resolves into two parts: first, that of the question of how an emulsion may be produced; and second, that of how, once the subdivision of the oil in the water has been accomplished, this subdivision may be or is stabilized. The two problems have not been kept apart as they should be. (See pages 26 to 27.)

Contrary to the general belief of different workers who have each tried to discover some one element to be responsible for this stabilization, a group of different factors evi-

dently plays a rôle, the relative importance of each factor varying not only in different emulsions, but in the same emulsion under different circumstances.

It is generally held that the formation and the maintenance of an emulsion depend upon the slight surface tension of the dispersing medium, and its high viscosity. While both of these factors undoubtedly play a part, their inadequacy in explaining the stability of all emulsions is generally admitted. Not only does the stability of emulsions not universally parallel the surface tension values of the liquids making up a given dispersoid, but dilute soap solutions with low viscosity act as better emulsifying agents than more viscid glycerin solutions. More recently the importance of a third factor has been emphasized in the maintenance of an emulsion, namely, the development of an encircling film about the droplets of the divided phase through the accumulation, in the surface between oil and dispersion medium, of finely divided particles of a third substance. But this explanation, too, seems adequate only for selected examples of emulsions. (See pages 27 to 29.)

In reviewing the empirical instructions available for the preparation of emulsions, and in our own attempts to formulate such as would always yield permanent results, we were struck with the fact that their production is always associated with the discovery of a method whereby the water (or other medium) which is to act as the dispersing agent is all used in the formation of a colloid hydration (solvation) compound. In other words, when it is said that the addition of soap favors the formation and stabilization of a division of oil in water, it really means that soap is a hydrophilic colloid which, with water, forms a colloid hydrate with certain physical characteristics, and that the oil is divided in this. The resulting mixture cannot, therefore, be looked upon as a subdivision of oil in water, but rather as one of oil in a hydrated colloid. (See page 29.)

Evidence is adduced showing that not only do all the

well known emulsification methods resort to the use of hydrophilic colloids, but conversely, through the use of any hydrophilic colloid a method is at once offered by which a lasting emulsion may be produced. Some of the materials commonly used for such purposes, and a discussion of such as may be used, are taken up in proof of this contention.

The use of different emulsifying agents, such as acacia, soap, egg yolk, egg white, blood albumin, casein, dextrin, gelatin, agar, etc., and their colloid-chemical behavior in the formation of colloid hydrates are analyzed from a colloid-chemical point of view. (See pages 30 to 31.)

The effects of the colloid itself, of its concentration, as well as the effects of variations in the concentration of the oil, are next discussed. The oil cannot be divided into a hydrated colloid until a certain lower limit of water content has been exceeded, nor can it be divided permanently into a hydrated colloid after an upper point has been passed.

The enumerated substances do not all act equally well. This is because, in the production of a hydrated colloid, they behave differently from both a qualitative and quantitative view-point. Best results are obtained with those substances which not only have the power of taking up much water, but which yield fairly viscid liquids with all amounts of water that may be added to them. What is wanted is a relatively homogeneous liquid of sufficient tenacity, by which is meant one that possesses good covering power together with great cohesiveness. (See pages 31 to 33.)

The action of casein as a stabilizing agent is particularly instructive. Neutral casein does not absorb much water and it does not in this form serve for the preparation of an emulsion. But when alkali is added, it develops marked hydrophilic properties, upon the appearance of which it becomes one of the best stabilizing agents for emulsions known. It might be thought that the alkali element is so important because it forms a soap in contact with oil, and soap has long been known as an effective emulsifier. While

some such action no doubt occurs, proof that the development of hydrophilic properties by the casein is of first importance is easily presented since acid (which when added to neutral casein converts it into a hydrophilic colloid) works quite as effectively as does alkali. (See pages 33 to 35.)

Emphasis is laid upon the great increase in viscosity which emulsions show when progressively larger amounts of oil are added to a given amount of a given colloid hydrate. Mixtures are prepared in this way which show maintenance of form, etc., in other words, the properties of solids, even though the constituent materials from which they were prepared are themselves liquid in nature. (See pages 35 to 44.)

III.

Generally speaking, emulsions are broken through the institution of conditions which are the reverse of those that make for their stabilization; in other words, whenever the hydrophilic (lyophilic) colloid which holds the aqueous dispersion medium is either diluted beyond the point at which it can take up all the offered water, or is so influenced by external conditions that its original capacity for holding water is sufficiently reduced. (See page 47.)

Certain emulsions, as those of oil in soap, therefore, tend to break on simple dilution. But agents which dehydrate the hydrophilic colloid act even more rapidly and effectively. What will prove to be an effective agent in this regard depends, of course, upon the character of the hydrophilic colloid stabilizing the emulsion. When alkali-casein is used, the addition of acid breaks the emulsion; while alkali will break an emulsion stabilized by acid-casein. The same concentration of acid or alkali is without effect upon an emulsion stabilized by a carbohydrate like acacia or dextrin. Since even neutral salts will dehydrate an acid- or alkali-protein, they readily serve to break emulsions stabilized by these substances. An emulsion of oil stabilized in soap is readily broken not only by acids and various

salts, but also by alcohol. Ether, on the other hand, is relatively ineffective. Practically all these substances in low concentration are without effect upon emulsions stabilized in hydrated carbohydrates.

The fact that alcohol and ether are by themselves thus relatively ineffective in breaking emulsions explains why the ordinary fat extraction methods are so often only partially effective in getting the fat out of biological materials, and why previous treatment of the material, as by digestion with strong acids or alkalies and by similar methods, yields higher fat figures than extraction with ether or allied materials alone. (See pages 47 to 53.)

IV.

The experiments on emulsions previously detailed are called upon in the interpretation of the biological behavior of the fat in the cells and in the secretions of animals and plants under physiological and pathological conditions.

The problem of the distribution of fat in living cells or in various secretions from the living tissues may be separated into two divisions: first, a chemical one dealing with such questions as that of the origin and transport of fat; and second, a physical one asking, for example, how smaller or larger amounts of fat may be stored in cells without at one time being visible or demonstrable by micro-chemical methods, while at another, as in "fatty degeneration," they are thus demonstrable.

There is scarcely a tissue or fluid of the body which, even in the poorest states of nutrition, does not contain some fat. But even the smallest amounts of fat thus found exceed the quantities that can be dispersed in permanent form in pure water. The presence of such amounts of fat in these structures, therefore, at once presents a problem identical with that which asks how it is possible, outside of the body, to maintain a fat in finely divided form in an aqueous dispersion medium. The presence of any amount of fat in a cell or tissue exceeding a fraction of one percent is possible

only because the tissues contain hydrophilic colloids. (See pages 57 to 62.)

Looked at from another point of view, even the smallest amounts of fat ever found in cells suffice to prove that the cell contents are not mere aqueous solutions of various salts and non-electrolytes contained in a semipermeable bag, as is so generally believed by the adherents of the osmotic conception of cell constitution.

How completely the notion that our cells are filled with salt solutions must go to pieces, becomes clearly evident when it is recalled that certain of our cells and tissues contain even normally some twenty percent of fat and fat-like bodies. Thus, of a hundred grams of nerve tissue, seventy grams are water and over twenty grams are fat. The remainder is protein chiefly. Nerve tissue and all tissues which, under normal or abnormal circumstances, hold such large quantities of fat are able to do so only because this material is stabilized in a finely divided state through the presence of hydrophilic colloids (like proteins and soap) which hold the water of the cells as a hydration compound. (See pages 62 to 64.)

The "solid" nature of many tissues with preservation of characteristic "liquid" properties may be explained through the emulsion character of the tissues. The "softening" of tissues observed in certain pathological studies may be understood as a return to the physical properties of the individual liquids making up the normal emulsion when this is "broken."

V.

While the fat in the cells of the body is not ordinarily visible in the state in which it exists here normally, certain pathological conditions popularly termed "fatty infiltration" or "fatty degeneration" suffice to make it readily visible. The older pathologists believed that more fat was thus visible for the reason that the cells had come to contain more, either because it had been brought to or stored

in the cells, or because their protein had been changed to fat. Modern studies of the question have proved the last of these possibilities to be entirely without foundation, so that now both "fatty infiltration" and "fatty degeneration" are, at the worst, held to be nothing more than states in which an excessive deposition may occur. But quantitative chemical studies have come to show that even the worst types of fatty degeneration in tissues may yield no fat figures lying beyond the amounts commonly found in these same localities under physiological conditions. In the majority of instances, chemical analysis fails to show that the affected cells contain any more than their normal fat content. In essence, therefore, "fatty degeneration" no longer represents a chemical, but a physical problem, which asks how a given quantity of fat usually so distributed in a cell as to be invisible, becomes re-distributed in such fashion as to be readily visible. (See pages 67 to 69.)

We believe this problem is identical with that of how an emulsion of oil in protein or soap, so fine that the individual oil droplets cannot be made out as more than granules even with high microscopic magnification, can be coarsened to the point where the fat granules will coalesce to form more readily visible droplets. As a matter of fact, detailed study of the conditions which are necessary for the production of typical "fatty degeneration" in tissues shows these to be identical with those which lead to the partial breaking and coarsening of emulsions of the type of oil-in-alkali casein, oil-in-soap, etc. (See pages 69 to 74.)

The various substances and conditions generally listed as capable of producing a "fatty degeneration" (phosphorus, lead, arsenic, mercury, alcohol, ether, chloroform, diabetes, local circulatory disturbances, intoxication with acids, etc.) are all of them means by which the normal hydration capacity of the soaps or of certain of the proteins of the cell (as the globulins) is markedly decreased. The matter is best illustrated, perhaps, by detailing a specific instance.

When a cell, in consequence of injury, is made the subject

of an acid intoxication by any of the direct or indirect means enumerated in the last paragraph, the acid makes some of the proteins of the affected cells swell, while another group (the globulins) is dehydrated and precipitated. The combination of swelling with precipitation yields what the pathologists call "cloudy swelling." But as the pathologists have long noted, a persistence of cloudy swelling is followed, almost as a rule, by a "fatty degeneration" of the affected cells. On the basis of our remarks, this coalescence of the oil droplets into the larger visible ones of "fatty degeneration" is dependent upon the removal, through the action of the acid, of some of the stabilizing effects of the proteins, soaps and other hydrophilic colloids contained in the cells. The increased swelling represents a dilution of the hydrophilic colloids of the cell, while the clouding represents a dehydration of certain others. (See pages 74 to 76.)

These studies on emulsions contribute toward the explanation of yet another pathological observation. When any tissue, as a portion of the brain, through some such pathological disturbance as a thrombosis, is deprived of its normal blood supply, the affected member shows first a cloudy swelling accompanied or succeeded by a "fatty degeneration," and then a "softening" of the tissues. How at least a portion of this (and, we are inclined to think, the major portion in such tissues as the brain) is brought about is illustrated in the changes in viscosity observable in the preparation of an emulsion or its subsequent destruction. Seven percent potassium soap and cottonseed oil, for instance, are both relatively mobile liquids, but when mixed in proper proportion, they yield an emulsion so stiff that it will stand alone. This is the analogue of the ten to twenty percent emulsion of fat and lipoid in hydrated protein which we call nerve or brain. If the oil-in-soap emulsion is broken through the addition of a little acid it yields an impure mixture of oil, water and precipitated colloid material — the analogue of the liquid contents found in any area of brain "softening." (See pages 76 to 85.)

VI.

The adipose tissues and fatty secretions receive separate consideration. With the exception of these two biological materials, protoplasm represents an emulsion of fat-in-hydrated colloid, and only under exceptional circumstances does the proportion of fat to hydrated colloid exceed twenty percent.

When the fat in an oil-in-hydrated colloid emulsion is steadily increased, a point is finally reached at which the emulsion breaks over to one of the opposite type, namely, one of hydrated colloid-in-oil. (See pages 89 to 91.)

In the case of the adipose tissues and of the fatty secretions, the fat figure rises to fifty, sixty, and even eighty-five or ninety percent. The adipose tissues, too, are emulsions, but the increase in the percentage of fat has been carried beyond the critical point and so they are emulsions of the type of water-in-fat. This fact accounts for the constant finding of several percent of water in the adipose tissues and fatty secretions. The reactions to paper, to feel, and to microscopic examination show the adipose tissues of the body and many of the fatty secretions to be emulsions of hydrated colloid-in-oil. How the change from the original type of oil-in-water emulsion, characteristic of ordinary cell protoplasm, to the type of water-in-oil, characteristic of adipose tissues and the fatty secretions, is brought about through progressive increase in the concentration of the fat is illustrated by the progressive change from the oil-in-water type of emulsion which we call milk into the water-in-oil type known as butter. Separation of cream, souring of the cream and churning are all methods which ultimately lead to concentration and coalescence of the fat droplets in the original milk to that emulsion of hydrated colloid-in-fat which we call butter. (See pages 91 to 95.)

The conclusions formulated in this field are then applied to the formation of ear wax and of other fatty secretions that are obtained from the oil-in-hydrated colloid proto-

plasm which makes up the secreting cells from which these secretions are obtained.) (See pages 95 to 96.)

The striking optical changes which accompany the gradual dehydration of the oil-in-hydrated colloid emulsion are commented upon and their importance in the interpretation of various biologic phenomena touched upon. (See pages 96 to 101.)

VII.

In passing from the ordinary tissue cell which represents a fine emulsion of fat in a hydrated protein, to the cell which is characteristic of the adipose tissues, essentially an emulsion of hydrated protein-in-fat, we observe the consequences incident to a progressive increase in the concentration of the fat in an oil-in-water type of emulsion to beyond the critical point. If we look at the results of the opposite type of change, namely that of increasing the amount of water in the ordinary fat-in-hydrated colloid which constitutes our cells, we find that this leads to the production of milk. (See page 105.)

Normal milk production represents just such a set of changes. The originally cubical cells which make up the alveoli of an active mammary gland become richer in water and filled with granules (cloudy swelling) while the fat in the cells runs together into more readily visible droplets (fatty degeneration). When this process of cloudy swelling with fat coalescence becomes sufficiently great, the cell bursts and a fluid mixture of hydrated colloids containing fat globules results. This is milk. (See pages 105 to 107.)

By making use of the laws governing the making and maintenance of emulsions, it is readily possible to make cow's milk or any other kind artificially, whenever the necessary chemical constituents are available. To do this it is only necessary to take the proteins characteristic of the milk desired, hydrate these to the point at which the natural fat of the milk (or some other fat) may be readily emulsified in them, and then dilute the mixture to the

necessary amount. To it may then be added the various salts, sugars, or other materials that are needed to give the milk its requisite composition. (See pages 108 to 111.)

VIII.

The ordinary view, that a secretion is not given off "as such" but that there is first a secretion of water which then leaches out from the secreting membrane the dissolved substances characteristic of the secretion, meets with difficulties when the secretion contains not only crystalloids (which readily diffuse through the colloids which constitute our secreting membranes) but the non-diffusing colloids. In an attempt to explain the production of the mucoid secretions, for example, it seems most probable that these are thrown off in practically non-hydrated form and then swell upon the surfaces of the secreting membranes when water is added to them. A model is described which illustrates this idea physico-chemically. Some acacia granules are ground in cottonseed oil. When a drop of this material is put under the microscope and a little water is permitted to come in contact with one edge of it, active surface movements begin and the particles of the acacia are thrown upon the surface of the oil droplet. Here they imbibe water and swell to form a mucoid mass covering the surface of the oil droplet.

The set of changes in this model and those observable in living cells are so strikingly alike that the suggestion seems justified that the forces active in the two are also much the same. (See pages 115 to 118.)

IX.

The problem of growth is divided by the experimental morphologists into two divisions: growth proper and differentiation.

The former is best defined as an increase in volume, the energy for which colloid-chemical study has found in the

swelling of the colloids of the involved cells, tissues or organs. When for internal or external reasons there occur inequalities in such swelling, stresses are produced which bring with them the first elements of differentiation in the growing protoplasm. Such differentiation is subsequently further and more obviously aided and abetted by changes in the physical state of the growing colloid masses as, for example, the precipitation of certain of the colloids. (See pages 121 to 123.)

A series of figures is shown illustrating the wealth of structure produced whenever simple hydratable colloids, mixtures of such, or emulsions containing different chemical constituents, are subjected to the stresses incident to drying, to the addition of water, or to the physical and chemical effects incident to the addition of various extraneous substances, etc.

Structures which are finely granular, coarsely granular and alveolar are described. Structures simulating growing connective tissue, involuntary muscle, or sarcoma are shown. How the fine markings of the skin, and how such apparently complex structures as carcinomatous pearls or whorls may be imitated is also touched upon. (See pages 123 to 138.)

A final paragraph shows how the protective coverings of plants, like those which make waterproof the leaves and fruits, may be formed through the drying of oil-in-water types of emulsions into the water-in-oil types. (See pages 138 to 140.)

X.

The final chapter attempts to point out the significance of the study of the emulsions for the problems of applied chemistry, of biology and of medicine.

By substituting definite laws for the empirical in the production, maintenance and destruction of emulsions, they are of importance to the pharmaceutical chemist, the purveyor of food, the dairyman and the manufacturer. By

touching upon the normal fat content of cells, the nature of "cell membranes," the state of the fat in the adipose tissues, the mechanism of the formation of the fatty secretions and that of the oily protective coverings characteristic of plants and animals, these studies are of importance to the biologist. By aiding in the explanation of the nature of fatty degeneration, and by thus contributing to a further analysis of what is reversible and what irreversible in the series of changes which characterize the reaction of protoplasm to injury, these emulsion studies are of interest to the thinker in modern medicine. (See pages 143 to 146.)

II. ON THE MAKING OF EMULSIONS.

II. ON THE MAKING OF EMULSIONS.

1. INTRODUCTION.

THE following pages are the outgrowth of the attempt, begun some years ago, to get an answer to the problem of the nature and causes of "fatty degeneration" and of certain biological phenomena which are closely associated therewith, like the formation of milk, the production of the oily secretions, and the origin of the protective coverings of plants. There appeared to us a rough analogy between the available facts covering these physiological and pathological processes and the behavior of emulsions. In following this lead more closely we observed, however, that there still existed great gaps in what had been written regarding the physics of the emulsions themselves. Since a knowledge at least of the main facts, if not of the whole theory, of the behavior of emulsions was requisite to our biological purposes, we found it necessary to go back to a study of the emulsions themselves.

The general problem of the deposition of fat in living cells and body fluids, under both physiological and pathological conditions, divides quite naturally into two parts: a first, concerned with the chemical question of the origin and transport of fat; and a second, dealing with the physical question of how large amounts of the substance may, at one time, be stored in a cell without being visible or demonstrable by micro-chemical methods, while the same amount, at another time, as in "fatty degeneration," is readily visible and easily demonstrable. This volume bears little upon the first of these problems; its main purpose is to indicate the illuminating help which the concepts of colloid chemistry may give the second.

Since all these biological problems are to our mind inti-

mately associated with those of the making, maintenance and breaking of emulsions, a study of the general physical chemistry of these systems is first in order.

The emulsions are of much interest from both practical and theoretical points of view. Not only do large quantities of economically important materials come to us in the form of emulsions (as milk, egg yolk, rubber, etc.), but the making and breaking of these is a matter of great economic and scientific concern. The problem of how an emulsion may be produced appears in the biological phenomena concerned with the formation of mammalian milk, the "milk" of plants, etc.; while that of the breaking of emulsions comes to us in the problems of butter manufacture, of the manufacture of emulsions used in therapeutics, in certain aspects of "fatty degeneration," etc.

2. DEFINITION AND TYPES OF EMULSIONS.

In its simplest form, an emulsion, as a mixture of two immiscible liquids, is a diphasic system. Since one liquid

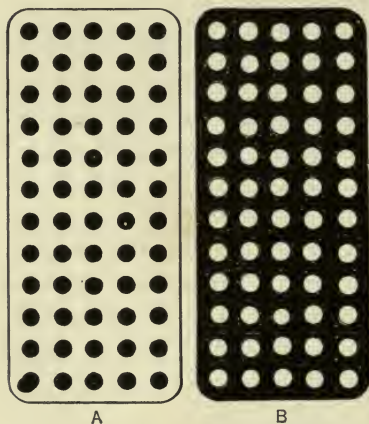


FIG. 1.

is subdivided in the other, an emulsion constitutes a dispersed system, according to the terminology of WOLFGANG OSTWALD.¹ Once the materials to make up an emulsion and their quantities are settled upon, it would seem, at first sight, of no consequence how these materials are divided into each other to yield the dispersed system. Definite quantities of water and oil, for example, would seem

destined always to yield the same end product. But as

¹ WOLFGANG OSTWALD: Handbook of Colloid Chemistry, 24, Trans. by FISCHER, OESPER and BERMAN, Phila., 1915.

indicated in the important studies of WALTHER OSTWALD¹ and T. B. ROBERTSON,² these materials are capable of forming *two entirely different kinds of emulsions: a first, consisting of oil in water, and a second, of water in oil.* In the former, the oil is the divided phase and the water the continuous one; in the second, the water is the divided phase and the oil the continuous one. The matter is illustrated diagrammatically under *A* and *B* in Figure 1. The two emulsions have totally different properties, as evidenced, for instance, by their different viscosities, by their different "feel" and by their different abilities to "wet" or "oil" paper dipped into them.

3. EXPERIMENTS ON EMULSIONS.

We shall take up now a more detailed study of a few emulsions in order to familiarize ourselves with their general properties. We chose for the purpose emulsions which, from a chemical point of view, consist of mixtures of oil and water. From a physical point of view they are, unless otherwise noted, of the "oil-in-water" type mentioned above, the oil being the divided phase, the aqueous dispersion medium the continuous, enveloping one. The oil referred to in these experiments is highly purified cotton-seed oil. Throughout the volume we speak of water as the second phase in our emulsions. As will be seen shortly, this is done for brevity, for, strictly speaking, it is not correct. These experiments will show that the aqueous phase is most commonly a hydration compound formed from combination of a protein, a soap, acacia gum, or some other hydrophilic colloid, with water, so that the emulsion under discussion becomes most frequently not a dispersion of oil in water, but one of oil in a hydrated soap, in a hydrated albumin, or something of the sort.

We know of no instance in which oil in contact with pure water or a watery dispersion medium leads *spontaneously*

¹ WALTHER OSTWALD: *Kolloid-Zeitschrift*, **6**, 103 (1910); **7**, 64 (1910).

² T. B. ROBERTSON: *Kolloid-Zeitschrift*, **7**, 7 (1910).

to the formation of an emulsion. In certain manufacturing processes, and under biological circumstances, conditions are sometimes instituted, or come to pass, which allow an oil to appear, or to be produced, in very fine particles which are then kept discrete. When milk is formed in nature, or when fat is deposited in cells through the combination of fatty acid with glycerin, the fat appears from the beginning in a state of fine subdivision and may be maintained thus. But under laboratory conditions, this fine division of a fat in a watery phase can be obtained only by mechanical methods.

We used such methods in our experiments. When small quantities of an emulsion are to be made, mortars do very well, as the pharmacists have long known. Larger quantities are better prepared in mechanical mixers of the type shown in Figure 2. The contents of the octagonal glass jar *a* are effectively beaten by the stiff stirrer *b* which may be turned at any speed desired by the pulley arrangement *c* connected by means of the belt *d* with a motor. When comparative experiments

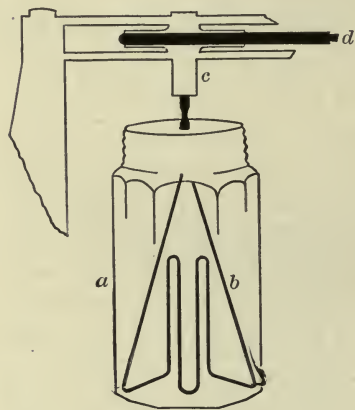


FIG. 2.

need to be done and conditions for mixing have to be kept constant, a series of mixers as constructed for us by our mechanican JOSEF KUPKA and shown in Figure 3 is run at the same speed by means of a continuous belt.

As will become better apparent later, the process of *making* an emulsion is something totally different from that of *maintaining* it after it is made. To make an emulsion showing a high degree of subdivision is not always easy. The accomplishment of the necessary mechanical subdi-

vision offers, at times, great difficulties. When light oils only are to be considered — as cottonseed oil or the lighter hydrocarbon oils — and an extreme grade of subdivision is not desired, the emulsifier of the type shown in Figure 2 will suffice. But if very fine emulsions are sought, the stir-



FIG. 3.

ring or rotary action of this device must be combined with *pressure*.

The reasons for this are about as follows: to divide a liquid, it must be torn. Any rotary motion will accomplish this to a certain extent. But if the rather large droplets thus produced are to be made smaller, the force producing the tearing must be increased. Speeding the rotary motion helps in this regard, but only to a certain point. It was EMIL HATSCHEK,¹ so far as we know, who first showed that the force required to divide a drop of any liquid mounts tremendously as the size of the droplet decreases. A rotary

¹ EMIL HATSCHEK: *Kolloid-Zeitschrift*, **6**, 254 (1910); **7**, 81 (1910).

motion acting upon liquid droplets floating in a second liquid does not therefore accomplish subdivision beyond a certain point. This point is determined by the kind and speed of the emulsifying flail, but much more by the viscosity of the oil to be divided and the viscosity of the medium into which it is being divided. When the dispersing medium is of a type to which, in a sense, the oil will "stick," allowing this therefore to be torn across the face of the dispersing medium, the best possible division of the oil is accomplished. The oil droplets are caught between the edge of the flail and a wall of stiff dispersing medium. Rotary motion therefore becomes reinforced by a cutting action and pressure. *Rotary motion combined with pressure leads to the greatest possible division.*

These considerations will show why, first of all, the old method of preparing emulsions in a mortar gave such good results. The rotary motion of the pestle is such as to tear any liquid (oil) over the face of the dispersing medium while

the pressure on the pestle aids in dividing the droplets more and more finely.

To get extreme division, a *homogenizer* is therefore of great service. Various designs of these have long been used in the dairy industry. Diagrammatic representation of the essential part of a pattern which in our hands yielded good results is shown in Figure 4. After a relatively coarse emulsion

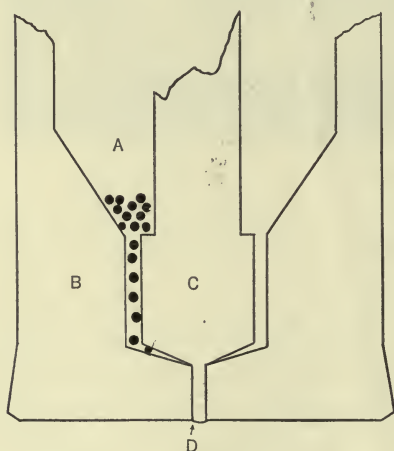


FIG. 4.

has been prepared by any convenient method, it is poured into the metal funnel A within which turns the pestle C upon which any amount of pressure may be exerted through a screw at the top.

To escape, the emulsion passes under hydraulic pressure between the grinding and pressure surfaces of *C* and *B*. Since these surfaces are bevelled, as shown in the diagram, the larger oil droplets entering above are gradually reduced in size before they are permitted to escape at *D* below.

4. ON THE MAKING OF EMULSIONS.

§1.

While the mere contact of cottonseed oil with water will not spontaneously lead to the formation of an emulsion, it is possible to produce this result by simply beating the two together. But the amount of oil that may be emulsified in pure water is very small. It suffices merely to impart a milky tinge to the water, and quantitative experiments indicate that less than one-half of one percent of cottonseed oil may thus be distributed into water with a fair degree of permanence. In Figure 5 is shown the effect of active agitation for 24 hours of 2 cc. of cottonseed oil in 98 cc. of distilled water. Within a few hours after the mixture is poured into a cylinder, almost the entire oil has separated out as a clear layer above the slightly milky water. No one has reported the permanent emulsification of oil in pure water in amounts exceeding two percent. This is the value obtained by



FIG. 5.

WM. C. McC. LEWIS¹ with mineral oil. The oil particles in these emulsions are rather small, their dimensions lying within the realm of the colloid degrees of division. These low concentrations of oil in water, therefore, really represent colloid suspensions of oil in water and possess not only the characteristic stability of such systems, but also their well-known saturation limit.²

As we ordinarily use the term "emulsion," we mean the subdivision of one fluid in a second in amounts exceeding these low values. The mixture must, moreover, show a fair degree of stability; in other words, the two liquids constituting the dispersoid must not separate in the course of weeks, months or years. A *temporary* subdivision of large quantities of oil in a given volume of water, or the converse, can, of course, be obtained by merely beating the two together. *The problem of emulsification, therefore, really resolves into two parts: first, the question of how an emulsion may be produced; second, how when once the subdivision of the oil in the water has been accomplished, this subdivision can be, or is, stabilized.* These two problems have not always been held apart as they should be. Failure to distinguish between them has given rise to purposeless and often bitter debate. In a certain sense the first of these two problems is essentially a mechanical one, upon the nature of which we have already touched, but since this mechanical problem is often intimately dependent upon, or connected with the physical properties of the medium into which the subdivision is being made, while these physical properties, in their turn, are connected with the question of the nature and the action of the various "emulsifying agents" used, it becomes readily intelligible why the two problems have been so constantly confounded. Having discussed the mechanical portions of the problem, we therefore turn to those con-

¹ WM. C. McC. LEWIS: Kolloid-Zeitschrift, 4, 211 (1909).

² For references to the literature dealing with this problem see WOLFGANG OSTWALD: Handbook of Colloid-Chemistry, 136, Trans. by FISCHER, OESPER and BERMAN, Phila., 1915.

cerned with the stabilization of the subdivision — in reality, that part of the general theory of emulsification upon which most effort has been expended by those who have busied themselves with this general subject.

Different workers have suggested different factors as the causes of the stabilization. Generally speaking, they have all striven to discover some one or two elements as exclusively responsible for it. We question whether this can be done successfully. While we wish to leave detailed discussion of the theoretical aspects of the problem to a later time when longer and more careful series of measurements have been made than are as yet available on the properties of various liquids which may be used successfully in the production of stabile emulsions, even such experiments as are now described by different authors, or have been made by ourselves, already indicate that a group of different factors plays a rôle, the relative importance of each of which varies not only in different emulsions, but in one and the same emulsion under different circumstances.

The most generally accepted factors that are held to be of great and general importance in the maintenance of an emulsion are those suggested by S. PLATEAU¹ and G. QUINCKE.² While these authors directed chief study to foams, the structure of these (as dispersions of a gas in a liquid) has usually been regarded as so closely related to that of emulsions (dispersions of one liquid in a second) that the conclusions reached from investigation of the one set of systems have been held applicable with little modification to the second.

PLATEAU and QUINCKE held the permanence of foams and emulsions to depend chiefly upon the slight surface tension of the dispersing medium and its high viscosity. While both these factors undoubtedly play a part, some obvious shortcomings in the theory have been emphasized

¹ S. PLATEAU: *Ann. der Physik.*, **141**, 44 (1870).

² G. QUINCKE: *Ann. der Physik.*, **271**, 580 (1888).

by H. W. HILLYER¹ and S. U. PICKERING.² Thus liquids, which from consideration of their surface tension would seem to be ideal for the production of permanent emulsions, fail in practice; and dilute soap solutions of relatively low viscosity, for example, turn out to be better emulsifying agents than more viscid glycerins. In this connection, HILLYER has made a fundamental contribution to the whole question by emphasizing that to obtain a proper measure of the surface tension relationships active in an emulsion, the surface tension of the dispersing phase must not be measured against air (which would be proper only in the case of air-foams) but against the second material entering into the composition of the emulsion (the oil).

PICKERING has brought out the importance of a third factor in the maintenance of an emulsion, namely, the accumulation of finely divided particles of a third substance in the surface between oil and dispersion medium. He assumes that these particles surround the oil droplets like a film. This, too, undoubtedly plays a part in the stabilization of a selected number of emulsions. Our personal objection to PICKERING's conclusions is only a quantitative one. In explaining the stability of such an emulsion as that of oil in soap, for instance, he needs to assume the soap always to be contaminated with stearin particles, a view that is hardly justified, for it is possible to obtain and work successfully with soap entirely free from such. WILDER D. BANCROFT³ is in sympathy with PICKERING's conclusions in that he also emphasizes the importance for stabilization of the formation of a third phase between the two materials emulsified in each other. This view of the importance of the production of an interfacial film which then keeps the dispersed particles from coalescing, is also accepted by G. H. A. CLOWES.⁴ Depending then upon

¹ H. W. HILLYER: Jour. Amer. Chem. Soc., **25**, 511 (1903); *ibid.*, **25**, 524 (1903).

² S. U. PICKERING: Kolloid-Zeitschrift, **7**, 15 (1910).

³ WILDER D. BANCROFT: Jour. Physical Chem., **17**, 501 (1913).

⁴ G. H. A. CLOWES: Jour. Physical Chem., **20**, 415 (1916).

changes in surface tension as induced through the addition of various chemicals, for example, CLOWES holds this film to be bent in the one or the other direction, thereby yielding in the one instance an oil-in-water type of emulsion, in the other one of water-in-oil.

§2.

In reviewing the empirical instructions available for their preparation, and in our own attempts to formulate such as would always yield permanent emulsions, we were struck with the fact that success in this direction is best attainable through the discovery of a method whereby the water (or other medium), which is to act as the dispersing agent, is all used in the formation of a colloid hydration (solvation) compound. In other words, an oil-in-water emulsion is markedly stabilized only through the addition of colloid to the watery phase. Empirically, this fact, too, has long been recognized although we question whether it has been fully understood what kind of colloid will produce stabilization and why this is effected. *An emulsion is stabilized only through the addition of a lyophilic (hydrophilic) colloid. The amount of colloid necessary is relatively great. It must be sufficient, at least in the production of an emulsion, to bind all the water if an emulsion showing real permanence is to be produced. Differently expressed, the production of a lasting emulsion, as of oil in water, is really never obtainable through the division of the former into the latter, but only through the division of the oil into a hydrated (solvated) colloid.*¹

¹ Both W. D. BANCROFT and G. H. A. CLOWES at the Urbana (1916) meeting of the American Chemical Society, in their discussion of our own views regarding the importance of colloid solvates (colloid hydrates) for the stabilization of emulsions, found in our views something irreconcilable with their notions of the importance of interfacial films and of surface tension changes in these. While we do not wish to insist upon a harmony where such may not be desired, there is, of course, nothing mutually exclusive in the ideas of solvation, of changes in surface tension, and — at times — the formation of a continuous third phase between the two chief substances making up an emulsion. When "water," according to our notion, becomes a "colloid hydrate," the properties of the second liquid are different from those

§3.

The truth of these assertions is best illustrated by investigating, from this colloid-chemical point of view, any of the empirically well-established methods generally used in the production of emulsions. A good illustration and one applicable to most oils is the following:

One part by weight of powdered acacia is ground in a mortar with two parts by weight of oil. To this is added slowly and with constant grinding, one part by weight of water. As the trituration is continued, a second part of water is stirred in and finally a third. This emulsion will then, in most instances, stand heavy further dilution with water without the oil separating out in coarse form.

This method yields an excellent emulsion. In reviewing the factors that contribute to this end, let it first be noted that the acacia used is a strongly hydrophilic colloid. Second, the amount employed is relatively high. In the terms of what was said above, at least enough colloid was used to *bind all the water*. The resultant emulsion is, therefore, in no sense to be regarded as one of oil in water but rather as one of *oil in a hydrated colloid*.

of the first, and these properties include surface tension, viscosity and distribution between two phases. But, we repeat, these factors to which PLATEAU, QUINCKE and PICKERING first directed attention are not by themselves able to explain all the phenomena observed. Where CLOWES holds that an emulsion of oil is stabilized through sodium oleate because the substance reduces the surface tension of water, we would say that stabilization has ensued because the oil has been divided into a highly hydratable sodium soap. When the addition of calcium destroys this emulsion, it is not because of complicated changes in a surface film, but simply because calcium oleate is an only slightly hydratable soap. Free water, in consequence, appears in the mixture, and the oil separates out in gross form, as described above, for only very little oil can be permanently subdivided in "pure" or "free" water. We describe the consequences of such changes from highly hydratable to less hydratable soaps upon the stability of an emulsion on page 49.

Neither do we wish our statement that an agreement is possible between CLOWES' and our views on simple emulsions to be expanded to include his beliefs regarding the biological behavior of the fat in living cells. We long ago gave up the notion of lipid membranes about cells and the complex notions of their changing permeability to which CLOWES and many authors still hold.

§4.

To test the view that it is really only the use of a hydrophilic colloid, and this in sufficient amount to bind all the water, that makes possible the preparation of a lasting emulsion, other colloids may be used in place of acacia. By the method outlined above, we have been able to make lasting emulsions with blood albumin, egg white and egg yolk (which in itself already represents an emulsion of oil in a hydrated protein colloid). We have also succeeded in preparing lasting emulsions by using aleuronat or casein as the hydrated colloid. If the temperature is properly controlled, gelatin may be used.

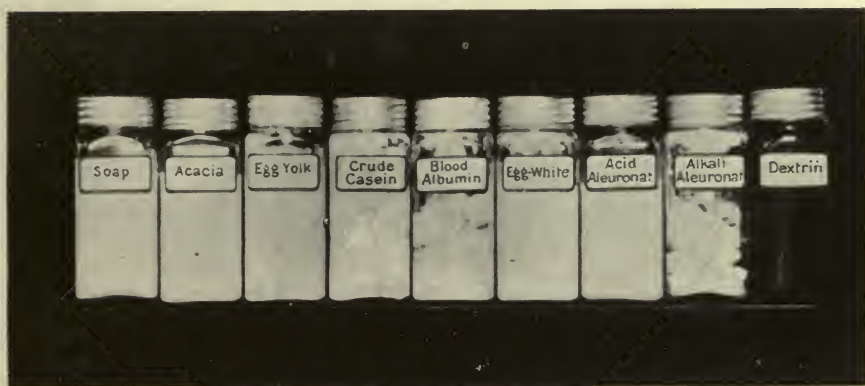


FIG. 6.

Not only may such proteins be used, but hydrophilic carbohydrates of various kinds also serve well. To the list beginning with acacia, we may add starch, dextrin (or the dextrinized starches used in baby foods) and, when the temperature is properly regulated, agar. A hydrophilic colloid which works exceedingly well, and to which we shall have occasion to return later, is soap. Emulsions showing a fair degree of permanence may also be prepared by dividing oil into concentrated (saturated) cane sugar solutions, or glycerin. The last named emulsions, however, tend to separate slowly in the course of days.

A photograph of a series of permanent emulsions prepared with some of these hydrophilic colloids is shown in Figure 6.

Reading from left to right, the jars contain permanent emulsions of cottonseed oil in soap, acacia, egg yolk, casein, blood albumin, egg white, acid-aleurinat, alkali-aleurinat, dextrin.

§5.

The substances enumerated in the last paragraph as capable of yielding hydrated colloids into which an oil may be divided successfully do not all act with equal ease. This is because they behave differently from both quantitative and qualitative viewpoints, so far as the production of a hydrated colloid is concerned, when they are mixed with water. Acacia, blood albumin, egg white, egg yolk and casein yield the best results. These substances not only have the power of taking up much water, but they form fairly viscid liquids and, what is of even more importance, of good *tenacity*¹ with all amounts of water added to them. Moreover, when the water is added, they yield relatively homogenous liquids and this occurs whether only a small amount is added or enough to make the colloid go into "solution." Furthermore, this whole set of changes accompanying the addition of progressively greater amounts of water may, in these particular substances, take place at one temperature (room temperature).

With colloids which do not so rapidly and effectively imbibe all the water offered them and which do not pass so easily and smoothly from the original viscid mixtures when small amounts of water are present, to the ultimate liquids approximating true solutions in character, greater difficulties are encountered in the preparation of stabile emulsions. The matter is illustrated in the case of starch in which, even after prolonged boiling, the individual, greatly swollen starch

¹ We mean by this the property of being stretched into thin threads or films without tearing. The oil globules need to be separated from each other by a liquid which, with great covering capacity, possesses also this high degree of cohesiveness. We are at present seeking for a method of measuring the values concerned in this problem in somewhat better fashion than is done, for example, by the ordinary "finger test" or by "glue testing" machines.

granules may still be discerned microscopically even when a small amount of starch has been boiled for a long time in much water. Emulsification in agar or gelatin also presents certain difficulties. Lasting emulsions of oil in gelatin are obtainable only by dispersing the oil in a gelatin mixture of a concentration which is just fluid at the temperature at which the experiment is carried out. If with such a gelatin colloid the temperature is raised (and its degree of hydration thereby decreased) a less permanent emulsion results. On the other hand, an emulsion of oil in gelatin remains fixed if the mixture is chilled to below the gelation point of the gelatin. The dextrans in their properties of forming hydrophilic colloids occupy a middle place between acacia, egg yolk or casein, on the one hand, and starch and gelatin, on the other.

§6.

The importance of the hydrophilic character of the colloid used in the preparation or stabilization of an emulsion is well illustrated in the case of casein. Neutral casein has practically no power of absorbing water, hence it has in this form no action in stabilizing an emulsion. When alkali is added to the casein, it develops marked hydrophilic properties, and as these appear, the power of the casein to stabilize also becomes manifest. While neutral casein with water and oil yields no emulsion, alkalinized casein does so at once.

It might now be urged that the real reason why the addition of alkali in this experiment yields an emulsion, lies in its effect upon the oil (with a consequent production of soap) rather than in its action upon the casein. This criticism can be met in striking fashion by using acid instead of alkali. Acid has no action upon fat, but when it is added to casein, the hydration capacity of the casein is increased just as when alkali is added. On *a priori* grounds it was, therefore, to be expected that the addition of acid to a casein-water mixture would prove just as effective in mak-

ing possible the emulsification of oil in it as had previously been noted in the case of alkali. Experiment shows this to be the case.

When to 5 grams of dry casein in each of three mortars (or stirring devices) there are slowly added, respectively, 50 cc. $\frac{1}{20}$ normal sodium hydroxid, 50 cc. water, 50 cc. $\frac{1}{20}$ normal hydrochloric acid, and, after sufficient time has been permitted to allow the casein to absorb all the water it will, into each are stirred 75 cc. of oil, the results shown



FIG. 7.

in Figure 7 are obtained. The mixture of the oil with the hydrated (alkali) casein in the jar on the left has yielded a perfect and permanent emulsion and the same result is observable in the case of the hydrated (acid) casein in the jar on the right. The middle jar shows an upper two-thirds of almost clear oil, below this a milky liquid containing microscopically visible particles of casein and fine oil droplets, and at the bottom a white layer of settled casein.

The importance of the hydrophilic properties of the colloid used in stabilizing a division of oil in water can often be

noted in a given mixture from which one is trying to make an emulsion. The addition of acid or alkali does not at once change the previously neutral casein of a given oil-water-casein mixture into the hydrated form and so one may not at once, with grinding in a mortar or stirring, succeed in getting an emulsion. Even an hour or two may not yield a good result. But if the mixture is simply left to itself for a while (as over night) the first stroke of the pestle suffices to start excellent emulsification. In the time allowed, the alkali or acid has acted upon the protein and the resulting compound, with its development of hydrophilic characteristics, has absorbed the "free" water previously present in the mixture. And as there is substituted for the originally tetraphasic system of

oil : water : casein : alkali

the diphasic one of

oil : hydrated-alkali-casein,

permanent emulsification becomes easy.

§7.

Either alkali- or acid-casein emulsions may be used to prove that emulsification in the protein is possible only as this contains a certain lower limit of water or does not exceed an upper limit.¹ When mixtures of unit amounts of casein and unit amounts of acid or of alkali have successively greater amounts of water added to them, emulsification upon the addition of unit volumes of oil does not begin until a certain value for the water has been exceeded. The first amounts of water make the casein swell into an exceedingly stiff, gum-like material. Not until enough water has been added to give it a syrupy consistency (at which time it will be found to stretch into long threads without breaking) or even a less viscid character, does the optimum for emulsification appear. When, on the other hand, too much water is added, the properties of the pure water again

¹ See page 22.

become prominent and then lasting emulsification again becomes difficult or impossible. The matter is illustrated in the following experiment.

Into each of five mortars are introduced respectively the following mixtures of casein, sodium carbonate and water.

	I.	II.	III.	IV.	V.
Casein.....	5 gm.	4 gm.	3 gm.	2 gm.	1 gm.
Sodium carbonate (Molar)	2 cc.	1.6 cc.	1.2 cc.	0.8 cc.	0.4 cc.
Water.....	20 cc.	20.4 cc.	20.8 cc.	21.2 cc.	21.6 cc.

After the mixtures have been allowed to stand for some hours, 10 cc. of oil are slowly stirred into each. In the first mortar no emulsification at all is obtainable; in the second, a partial result is obtained; the third mortar gives a fairly good emulsion and the fourth a perfect one. In the fifth mortar only a coarse, but fairly stabile, division of the oil in the hydrated colloid is obtainable.

These experimental results will serve to emphasize again that there exists a difference between the possibility of *producing* an emulsion in a given alkali-casein (or other hydrated colloid) and its *maintenance*.¹ When, for example, oil is being ground or stirred into the hydrated casein, an optimum concentration can be discovered in which this grinding or stirring proves most effective in subdividing the oil. As has been noted by different authors, the emulsification process is then likely to emit a characteristic crackling sound. In other words, *for the production of the emulsion certain optimal mechanical conditions are required*. On the other hand, *when once a good emulsification has been thus obtained, heavy further dilution with water will not break the emulsion*, even though in such a dilute colloid medium the emulsification could not have been successfully produced in the first place.²

¹ See page 26.

² See in this connection page 108 on the making of milks.

§8.

Soap has long served as one of the best of materials with which to favor the stabilization of a finely divided oil in water. In confirming this well-known fact through our own experiments we should like to emphasize that the action of the soap is probably decidedly simpler than is generally assumed. To permit the formation of a permanent emulsion, a definite and rather high concentration of soap must be used. Let it be noted that soap in such concentrated form is a typical hydrophilic colloid. The formation of an emulsion by dividing oil into such soap is again merely the process of dividing oil into a hydrated colloid.

What was said above regarding the concentration of the water in the acid- or alkali-casein holds also for soap when thus viewed as the hydratable colloid. Oil cannot be successfully divided into a soap of too high concentration like the stiff potassium soap which comes to us in the market as the ordinary "soft soap." More dilute "solutions" of this soap work much better. On the other hand, too dilute solutions also fail not only in the successful production of an emulsion but in the stabilization of the emulsion after this has been formed. This is easily seen in such a series of experiments as is photographed in Figure 8. Each of the mixtures contains water (20 cc.) and oil (120 cc.). The first cylinder on the left contains water and oil only. The remaining vessels contain the same amounts of water and oil; but before the oil was beaten into it, there were added to the water different amounts of soap so that the resulting soap-waters had the successive concentrations from left to right of 0.625, 1.25, 1.875 and 2.5 percent. When first poured into the jars shown in the illustration, after an hour's beating in the stirring apparatus, the mixtures look much alike. The pure water and oil mixture separates very quickly. In the course of the next 48 to 56 hours, separation occurs in some of the others. The photograph was taken at the end of several days. Separation in the

first cylinder on the left, containing oil and water only, is practically complete; the same is true for the second, containing but little soap, and for the third, which is partially broken; the fourth cylinder showed separation after several days, while the fifth yielded an entirely permanent emulsion.

But the soaps tend to lose their hydrophilic properties on mere dilution. In keeping with this fact, an increasing



FIG. 8.

difficulty is noted in the production of an emulsion as the soap is diluted. Lasting emulsions cannot be prepared in a soap water below a certain concentration; more technically put, enough hydrophilic colloid must be present to take up all the water as a hydrate before stabilization is obtained.

These facts make it clear, therefore, that for the stabilization of an emulsion, there exists an optimum in a region of medium concentration of any hydrophilic colloid—it must be neither too concentrated nor too dilute. We emphasize

the matter here because of the biological applications that are to be made of it later. It is in these middle concentrations that the soap (or other colloid) shows its greatest covering power with a high degree of cohesiveness. In other words, the hydrated colloid may here be stretched to the greatest possible degree without rupture.

Another fact which it is of great interest to note at this time is the composition of the various layers which are formed whenever (as in the second jar from the left in Figure 8) separation occurs for any reason. Four layers are clearly visible. Uppermost is a layer of pure oil which shows black in the photograph; below this comes a second (white) oil layer containing a fine dispersion of the aqueous (soap-water) phase; next comes soap-water containing a fine dispersion of oil; at the bottom is (practically) pure soap-water. Each of the two main divisions of oil and soap-water, therefore, remains contaminated for a long time with a small amount of the opposite phase.

§9.

It is of interest next to consider the effects of beating



FIG. 9.

different amounts of oil into a given quantity of soap solution of known concentration. The effect with smaller

amounts of added oil is shown in Figure 9. Each of the jars in which the emulsions were prepared contained originally 25 cc. of 25 percent potassium soap and into them were stirred, in slow successive additions, larger and larger quantities of cottonseed oil. In the five bottles of Figure 9 are shown the effects when 20, 30, 40, 50 and 60 cc. of the oil are added. The jars were photographed after they had stood some 24 hours following the mixing. Permanent emulsification has occurred in all, but, as clearly evident, the oil droplets still rise like a cream to the surface in the first four of the jars. It requires some 60 cc. of oil before the soap is used up sufficiently to prevent its slipping to the bottom from between the oil droplets.



FIG. 10.

The point to be particularly emphasized in connection with the experiments partially illustrated in this photograph is that the *viscosity of the different emulsions also rises from left to right*. Much greater quantities of oil can be beaten into the amount and concentration of soap chosen for this series. As this is done, the resulting emulsion becomes progressively stiffer until finally it will no longer flow. The jar may then be turned upside down without the contents flowing out. Such a high viscosity is obtained when, to the standard amount and concentration of soap, 150 cc. or more of oil are added. The great viscosity of the resulting mixtures is graphically demonstrated in Figure 10. These emulsions with their high oil content can

not only be partially moulded and hold the shapes given them, but a metal wire thrust vertically into each will remain in an upright position.

With still further additions of oil, a critical point is finally reached beyond which no more oil can be divided into the soap. If the attempt is made to do so, *the oil is seen to separate out and the whole mixture to go over into the second type of emulsion, namely, one of soap water-in-oil.* Under the conditions of our experiments, the transition point is reached when about 470 cc. of oil are beaten into 25 cc. of soap solution. As the oil separates, the viscosity of the mixture falls, resulting in a fluidity more nearly that of oil itself.

§10.

Because of the biological applications that will subsequently be made of them, it is of interest to study the microscopic appearances of these emulsions. The failure to satisfy the mechanical requirements previously discussed makes it hard to get more than a coarse emulsion when oil is beaten into a relatively large amount of soap solution. This is shown in Figure 11 which is a photo-micrograph of a drop of the emulsion containing 20 cc. of oil and shown in the left-hand jar of Figure 9. Figure 12 shows a closer packing of the oil droplets with less free hydrated-soap between them. This is a preparation taken from the emulsion containing 60 cc. of oil and shown on the extreme right of Figure 9. When optimal conditions for the division of the oil in the soap are offered (as with still higher additions of oil), the oil droplets become so fine that they appear as mere granules, even when magnified many hundreds of times. Figure 13, showing an approximation to this state, is taken from a mixture of 300 cc. of oil in 25 cc. of 25 percent soap. When oil is added to the breaking point, the picture shown in Figure 14 appears, in which streaks of clear oil are seen between the islands of oil-in-soap emulsion.

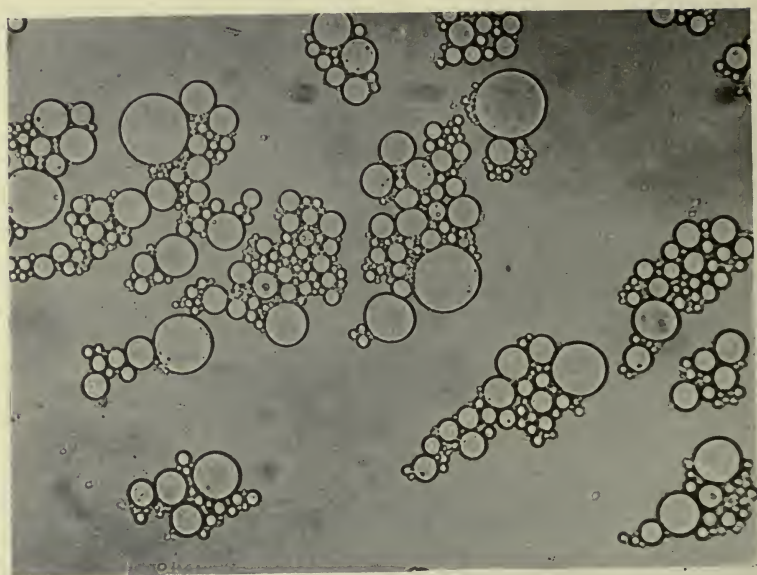


FIG. 11.



FIG. 12.

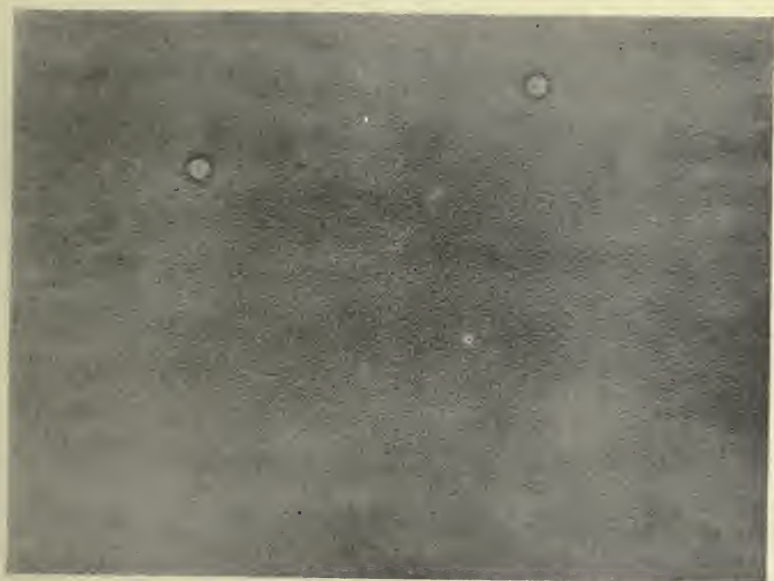


FIG. 13.



FIG. 14.

§11.

The behavior of saturated cane sugar solutions and of glycerin deserves comment. While the great viscosity of these solutions comes to mind as the first element determining the stability of emulsions prepared from them, it must not be forgotten that both are possessed of properties indicative of a certain degree of colloidality. Not only does their viscosity by itself indicate this, but, as is well known, these substances show the TYNDALL phenomenon.

III. ON THE BREAKING OF EMULSIONS.

III. ON THE BREAKING OF EMULSIONS.

1. THE GENERAL RULE.

AFTER what has been written above regarding the making and the maintenance of emulsions, we can be brief regarding the means by which they may be broken. *An emulsion breaks whenever the hydrophilic (lyophilic) colloid which holds the aqueous dispersion medium is either diluted beyond the point where it can take up the added water, or is so influenced by external conditions that its original capacity for holding the aqueous dispersion medium is sufficiently reduced.* After these fundamental conditions have been established, certain accessory requirements, which will be touched upon immediately, must also be satisfied in order that the breaking may occur, but they are, on the whole, of a minor character.

2. ILLUSTRATIVE EXPERIMENTS.

§1.

The fact that simple *dilution* will serve to break an emulsion is best illustrated in those cases in which the hydrophilic (lyophilic) colloid is readily "soluble" in the water (or other pure dispersion medium). Soap emulsions or certain protein emulsions, therefore, work best in this regard. In making the dilution, care must be taken really to wash the oil globules by thoroughly mixing the emulsion with the pure dispersion medium. The oil globules then rise to the surface and coalesce to form a continuous oil layer. In Figure 15 is shown the effect of simply adding water to what was originally a perfectly stabile oil-in-soap emulsion. The first bottle on the left contains the unit quantity of standard oil-in-soap emulsion (120 cc. oil in 20 cc. 7 percent potassium soap). The remaining bottles

contain the same amounts of emulsion to which have been added successively larger amounts of distilled water. The



FIG. 15.

photograph was made 48 hours later. As clearly evident, the addition of enough water led to breaking, as illustrated in the two bottles on the right of the photograph.

§2.

The breaking of an emulsion is also easily accomplished through the *addition of those substances which destroy or dehydrate the hydrophilic colloids* that give an emulsion its original stability. The substances that will prove effective in this regard are, of course, many and different, depending upon the nature of the hydrophilic colloid. An illustrative series covering oil-in-soap emulsions is shown in Figure 16.

The first bottle on the left shows the unbroken (control) emulsion. As was to be expected, an oil-in-soap emulsion is readily broken by acids, as shown in the second bottle from the left of Figure 16. The added acid combines with the base of the soap and liberates its fatty acids. Since neither of the products thus formed has the marked hydrophilic properties of the original soap, the water originally held as a hydrate is freed. A rapid separation of the emulsion



FIG. 16.

follows, for, as we noted before, not more than a fraction of one percent of oil can be permanently emulsified in pure water.

The addition of an equal amount of alkali in the form of potassium or even sodium hydroxid is without effect in bringing about a breaking of the emulsion. This is shown in the third bottle. Yet if the same amount of alkali is added as calcium hydroxid the emulsion separates. The explanation of this fact, which is illustrated in the fourth bottle of Figure 16, is as follows. The soaps of potassium, sodium and calcium possess hydrophilic prop-

erties in very unequal degrees. Potassium soap can hold so much water that it remains a "soft" soap under ordinary circumstances. Sodium soap has also the power of absorbing much water, though markedly less than potassium soap. Sodium soap is therefore the ordinary soap of commerce. Calcium soap holds so little water that we cannot wash with it. When to an emulsion of oil in potassium soap we add potassium hydroxid, nothing happens. Even when we add sodium hydroxid, the new sodium soap formed may still hold enough water to yield the hydrated colloid in which alone the subdivided oil may be stabilized. But when we add calcium hydroxid, the resultant calcium soap holds so little water that "free" water appears in the emulsion and so the oil droplets begin to run together.

The hydrophilic properties of potassium soap may be reduced not only by making some other soap out of it, but through the addition of sufficient amounts of different salts. The addition of enough salt, therefore, is likely to lead to separation in an oil-in-soap emulsion. The fifth and sixth bottles from the left in Figure 16 will serve to illustrate the matter. To the fifth bottle, calcium chlorid was added; to the sixth, sodium chlorid.

The effect of the anesthetics alcohol, chloroform and ether upon oil-in-soap emulsions is not without interest. Alcohol brings about a rapid separation of the phases. The soap dissolves in the alcohol, but at the same time loses its lyophilic properties. The water is, in other words, separated from its colloid combination, and as this occurs, the oil droplets begin to flow together and to separate out in gross form. Chloroform has much the same effect when enough is used and leads ultimately to a slow breaking of the emulsion. A fact not without interest for our further discussion is that ether has hardly any effect in this direction.

The effects of these three fat solvents are shown in the three bottles on the right of Figure 16. While we would not be understood as finding in this behavior a complete explanation of the relative toxicity of these different sub-

stances when used as anesthetics upon living protoplasm, it is of interest to note that the order of their action upon these emulsions does parallel clinical experience.

In the case of an emulsion of oil stabilized in alkali-casein, the addition of a little acid breaks the emulsion; while alkali proves effective in this regard if acid-casein has been used in making the emulsion. As noted several years ago,¹ various salts — even the neutral salts — exert a dehydrating effect upon a protein hydrated through the presence of an acid or an alkali. The salts that are active in this regard act in identical fashion both from a quantitative and a qualitative point of view when added to these emulsions, breaking them whenever they bring about a requisite degree of protein dehydration with the separation of water in "free" form. Ether, chloroform and alcohol all tend to break emulsions of oil stabilized in protein and about in the order given, the first named acting most powerfully. There might at first sight seem to be something contradictory between these facts and those mentioned in the previous paragraph together with the biological analogies to the phenomena of anesthesia. This, however, is not the case. We speak here of certain gross physical and *direct* effects which the anesthetics have upon just such emulsions as we shall see later exist in our tissues. But in living animals the anesthetics also have *indirect* effects. For example, they lead to an abnormal production and accumulation of acids in the body — a problem which EVARTS GRAHAM² has recently studied to splendid advantage — and these acids then produce secondary physico-chemical and biological effects which entirely obscure the primary physical effect under discussion here.

The emulsions hardest to break are those in which the

¹ See MARTIN H. FISCHER and GERTRUDE MOORE: *Am. Jour. Physiol.*, **20**, 330 (1907); *Pflüger's Arch.*, **124**, 69 (1908); *ibid.*, **125**, 99 (1908); see also, MARTIN H. FISCHER: *Edema and Nephritis*, 2nd edition, 46, New York, 1915.

² EVARTS GRAHAM: *Jour. Exp. Med.*, **22**, 48 (1915).

carbohydrates like acacia, dextrin or starch have been used to produce the stabilization. Acids or alkalies in moderate concentrations are without effect upon them. This is because in the concentrations used, these materials have practically no action upon these carbohydrate hydration compounds. The same may be said regarding the effects of salts, alcohol, chloroform or ether, which in other emulsions produce such marked effects. The emulsions stand, therefore, in spite of the addition of these various substances.

This great stabilizing effect of the colloid carbohydrates will also aid us, we believe, in the understanding of certain problems associated with the anesthetics and with the effects of other poisons in the body. The tissues are less easily poisoned by the anesthetics, for instance, when glycogen is present in the cells. In trying to explain this fact, it is well to remember that the presence of this colloid carbohydrate and of other carbohydrates like it tends to stabilize oil-in-protein and oil-in-soap emulsions against the effects of various added substances which would otherwise destroy the emulsions.

§3.

To this list of the methods by which an emulsion may be broken should be added the effects of mere *drying*. Just as oil cannot be divided into a hydrated colloid until this has come to contain a certain minimum of water, just so the resultant emulsion will separate again if, after it is prepared, the water is allowed to evaporate from it. This may be observed very well in oil-in-soap emulsions or oil-in-hydrated protein emulsions which separate into oil and concentrated colloid residues as soon as they are permitted to dry sufficiently.

3. SPECIAL CONSIDERATIONS.

A final word should be added regarding certain accessory conditions which need to be satisfied in order to accomplish the breaking of an emulsion. In order that the oil droplets may coalesce, they must be brought into physical contact with each other. For this reason, emulsions containing a high concentration of oil tend to break more easily, more quickly, and more perfectly than less concentrated ones. Very dilute emulsions tend to hold for long periods of time. Coarsely divided oil particles, moreover, coalesce more easily than do those more finely divided.

Following the general laws governing the distribution of a third material between two phases, an emulsion will frequently stand heavy dilution with water or the addition of materials which dehydrate the stabilizing colloid without breaking, if the colloid material either is from the first, or comes to be, concentrated in the surface between the oil globules and the aqueous phase.¹ This is why oil-in-protein emulsions (the milks, for example), resist the addition of water and will not break easily even when powerful dehydrating agents are added to them. It also explains why the addition of suspension colloids or their production (as in the case of the finely divided metals) in an oil-water mixture gives the emulsion a fair stability. Through such *adsorption* effects and the protecting films thereby drawn over the oil globules, these may be kept from coalescing even though every other opportunity is offered them to do so. It is only for this reason that dilution alone does not suffice to break *every* emulsion.

¹ See in this connection S. U. PICKERING: *Kolloid-Zeitschrift*, **7**, 15 (1919).

IV. ON THE NORMAL FAT CONTENT OF CELLS.

IV. ON THE NORMAL FAT CONTENT OF CELLS.

1. THE GENERAL FACTS.

WE are now in a position to use the experiments on emulsions detailed in the previous sections for the interpretation of certain of the problems associated with the history of fat in biological material.

It may be stated as generally true that all cells and fluids of the body contain fat and fat-like substances. The amount that they contain varies greatly not only in a given cell or body fluid under different physiological or pathological circumstances, but at all times in the different cells and fluids. Certain of the body cells, for example, contain at no time more than slight amounts, while others may show the enormous values characteristic of the adipose tissues. But even the slight amounts found in fat-poor cells or body fluids suffice to raise the biologically important question of how even these may be and are carried.

In order to obtain a first and rough insight into the whole problem, let us view the classic figures of E. BISCHOFF.¹ In his chemical analysis of a thirty-three year old man, he found the body as a whole to contain 58.5 percent water, 18 percent fat and about 20 percent protein. From this total fat figure we shall subtract one-half, or even two-thirds, as contained in the readily separable adipose tissues of the body. The question of the fat in these tissues receives individual study later.² But even after we have made this liberal subtraction, several percent (and these calculated in terms of the *moist* weight of the body) still remain hidden in discrete form in the rest of the tissues

¹ E. BISCHOFF: Vierordt's Daten und Tabellen, 187, Jena, 1888.

² See page 89.

and fluids of the body. By what means is this made possible?

As a matter of fact, the problem is not as simple as these average figures would seem to indicate; when for these there are substituted those actually observed in the analysis of individual organs, it is found that the fat content, instead of amounting to a few percent, rises, in some instances, to a quarter of the total moist weight of the cells. Table I, taken from GORUP-BESANEZ,¹ illustrates this. The values are in nearly all cases too low, for they date from a time when the better methods of fat analysis now available were unknown.

TABLE I.

PERCENTAGE OF FAT IN DIFFERENT FLUIDS AND ORGANS OF THE BODY.

Sweat.....	0.001	Cartilage.....	1.3
Vitreous humor.....	0.002	Bone	1.4
Saliva.....	0.02	Crystalline lens.....	2.0
Lymph.....	0.05	Liver.....	2.4
Synovial fluid.....	0.06	Muscle.....	3.3
Amniotic fluid.....	0.06	Hair.....	4.2
Chyle.....	0.2	Brain.....	8.0
Mucus.....	0.3	Nerve.....	22.1
Blood.....	0.4		
Bile.....	1.4		
Milk.....	4.3		

¹ GORUP-BESANEZ: Quoted by W. D. HALLIBURTON, Schäfer's Text-Book of Physiology, 1, 17, Edinburgh, 1898.

Table II may be added in illustration of further analyses in this direction.

TABLE II.

PERCENTAGE COMPOSITION OF DIFFERENT BODY FLUIDS AND TISSUES.

	Water.	Fat and Lipoid.	Protein.	Ash.
Dog serum ¹	93.60	0.68	4.52	0.87
Dog chyle ¹	90.67	6.48	2.10	0.79
Dog chyle.....		.25 to 14.6 ²		
Synovial fluid ³	93.08	0.87	5.20	0.85
Lens ⁴	63.50	0.74	34.93	0.82
Rabbit muscle.....	75.10 ⁵	1.07 ⁶	16 to 20	
Prairie chicken muscle.....		1.43 ⁶		
Human muscle ⁷	73.50	2.27	20.01	3.12
Animal retinas ⁸	86 to 90	1.27 to 4.13	5.71 to 8.45	0.69 to 1.2
Leucocytes ⁹	88.51	2.00	8.00	1.11
Calf thymus.....		1.37 ¹⁰		
Ox thymus.....		16.80 ¹⁰		
Fresh bone ¹¹	50.00	15.75	11.40	21.85
Veal liver ¹²		5.30	19.00	1.30
Egg yolk ¹³	47.19	35.31	15.63	0.97

¹ F. HOPPE-SEYLER: Quoted by E. A. SCHÄFER, Schäfer's Text-Book of Physiology, **1**, 183, Edinburgh, 1898.

² ZAWILSKY: Cited by H. VIERORDT, Daten und Tabellen, 154, Jena, 1888.

³ SALKOWSKI: Quoted by E. A. SCHÄFER, Schäfer's Text-Book of Physiology, **1**, 184, Edinburgh, 1898.

⁴ LAPTSCHINSKY: Quoted by W. D. HALLIBURTON, Schäfer's Text-Book of Physiology, **1**, 123, Edinburgh, 1898.

⁵ J. RANKE: Quoted by OTTO NASSE, Hermann's Handbuch d. Physiologie, **1**, 1 ter Theil, 284, Leipzig, 1879.

⁶ J. KÖNIG and B. FARWICK: Quoted by OTTO NASSE, Hermann's Handbuch d. Physiologie, **1**, 1 ter Theil, 283, Leipzig, 1879.

⁷ W. D. HALLIBURTON: Schäfer's Text-Book of Physiology, **1**, 95, Edinburgh, 1898.

⁸ CAHN: F. HOPPE-SEYLER's Physiol. Chem. 699, Berlin, 1881.

⁹ LILIENFELD: Quoted by W. D. HALLIBURTON, Schäfer's Text-Book of Physiology, **1**, 82, Edinburgh, 1898.

¹⁰ FRIEDLEBEN: Quoted by F. HOPPE-SEYLER, Physiol. Chem. 721, Berlin, 1881.

¹¹ F. HOPPE-SEYLER: Quoted by W. D. HALLIBURTON, Schäfer's Text-Book of Physiology, **1**, 111, Edinburgh, 1898.

¹² ATWATER and BRYANT: Quoted by W. H. HOWELL, Text-Book of Physiology 938, 6th Edition, Philadelphia, 1915.

¹³ PARKE: Quoted by F. HOPPE-SEYLER, Physiol. Chem., 782, Berlin, 1881.

The composition of some of those tissues which, exclusive of the purely adipose tissues, show the highest figures in the matter of fat content, is emphasized in Table III.

TABLE III.
PERCENTAGE COMPOSITION OF NERVE TISSUE.

	Water.	Dry Matter.	Percentage Composition of Dry Matter.			
			Fat and Lipoid.	Pro-teins.	Other Materials.	Salts.
Gray-matter of ox brain (PETROWSKY ¹).....	81.60	18.40	36.45	55.37	6.71	1.45
White-matter of ox brain (PETROWSKY ¹).....	68.35	31.65	71.36	24.73	3.34	0.57
Human spinal cord.....	74.84 ²	25.16	75.1 ³	23.80		1.1
Human sciatic nerve.....	58.33 ⁴	41.67	56.09 ⁵	36.80	7.07	

¹ PETROWSKY: Pfüger's Arch., 7, 367 (1873).

² E. BISCHOFF: Vierordt's Daten und Tabellen, 187, Jena, 1888.

³ MOLESCHOTT: Quoted by W. D. HALLIBURTON, Schäfer's Text-Book of Physiology, 1, 116, Edinburgh, 1898.

⁴ E. BISCHOFF: Vierordt's Daten und Tabellen, 187, Jena, 1888.

⁵ JOSEPHINE CHEVALIER: Quoted by W. D. HALLIBURTON, Schäfer's Text-Book of Physiology, 1, 116, Edinburgh, 1898.

2. PROTOPLASM AS AN EMULSION.

These three tables suffice to show that even those fluids and tissues of the body which are poorest in fat may already show values which lie beyond the limits of the amounts that may be "dissolved" or suspended permanently (in colloid form) in pure water. And when the high fat values characteristic of some of the tissues are reached, the possibility of considering the problem as identical with that of the mere division of oil in water disappears entirely.

The fats can be held in such high amounts in the cells and fluids of the body only because they are emulsified in the cell protoplasm. Were the generally accepted notions correct, according to which cells are mere osmotic bags made up of a surrounding semipermeable membrane within which is held an aqueous solution of salts and various non-electrolytes, it would be impossible ever to find in them, in permanently subdivided form, more than a fraction of one

percent of fat. *The reason why living cells are readily able to hold amounts of fat exceeding these low values and even to the point where they make up twenty-five percent of the total (moist) cell substance is because the cells are composed for the most part of hydrophilic colloids.* As hydrated colloids are able to stabilize the division of an oil in an aqueous medium, just so do the hydrophilic proteins, soaps and carbohydrates existing in the tissues and their secretions make it possible for these to hold the large amounts of fat found in them in permanently subdivided form.

Tables II and III (as well as the now extensive evidence¹ available indicating that the dominant factor determining the amount of water held by protoplasm under normal and abnormal circumstances is found in the colloid behavior of the proteins) show that the most important hydrophilic colloids concerned in stabilizing the normal fat content of the different tissues and fluids of the body, come from the class of the proteins. The proteins need not and do not, however, play an exclusive rôle in this direction. Not only is it to be suspected that the various hydrophilic carbohydrates must play some part (especially in plants), but the soaps, so often appearing under normal and abnormal circumstances in various cells and secretions, must also be considered. The high soap content of bile, for example, may well be the chief agent keeping the fats and lipoids so constantly found in this secretion from separating out in gross form.² The analytic figures of B. MOORE³ contained in Table IV illustrate the matter.

¹ See MARTIN H. FISCHER: *Physiology of Alimentation*, 187 and 267, New York, 1907; *Am. Jour. Physiol.*, **20**, 330 (1907); *Pflüger's Arch.*, **124**, 69 (1908); *ibid.*, **125**, 396 (1908); *ibid.*, **127**, 1 (1909); *ibid.*, **127**, 46 (1909); see also the several papers since in the *Kolloid-Zeitschrift*. A running account is found in *Edema and Nephritis*, 2nd edition, New York, 1915.

² The important bearing that these considerations have upon the mechanism of gall-stone formation (cholesterin stones, for example) is self-apparent.

³ B. MOORE: *Schäfer's Text-Book of Physiology*, **1**, 370, Edinburgh, 1898.

TABLE IV.
PERCENTAGE COMPOSITION OF BILE.

	Fats and Lipoids.	Soap.	Taurocho- lates.	Mucin.	Other Or- ganic Materials.
Gall bladder bile.....	5.982 1.146	3.155 0.104	11.959 12.602	0.454 0.245	0.973 0.274
Liver bile.....	0.527 0.409	0.127 0.110	3.460 3.402	0.053 0.170	0.442 0.543

3. BIOLOGICAL CONSEQUENCES.

These considerations would seem to compel the conclusion that under normal circumstances the fat found in the body cells and fluids is there in finely divided form and is kept so through the agency of various hydrated colloids (proteins, carbohydrates and soaps). In thus pointing out the parallelism existent between various tissues and fine emulsions, we obtain at the same time an understanding of certain other phenomena familiar from study of biological materials.

§1.

When a yellow oil, like cottonseed oil, is divided into a practically colorless liquid like a soap or protein solution, the mixture becomes brilliantly white. The white color of the white matter of the brain, and the whiteness of nerve tissue, may be regarded as expressive of the same type of subdivision of fat and lipid into the hydrated protein (chiefly) which makes up the rest of these anatomical structures.

The fact, moreover, that even such large amounts of fat as may be present in certain tissues (like those of the brain and peripheral nerves) need not betray themselves optically or to the ordinary fat stains like Sudan III and osmic acid is also identical with the behavior of such fine emulsions as may be prepared experimentally. Emulsions may be made so fine that refraction effects no longer suffice to bring out

the oil droplets and such staining methods fail to demonstrate the presence of fat.

§2.

A matter of biological importance for the theory of cell structure is contained in the question of whether, normally, the fat in a cell constitutes the divided phase and the hydrated colloid making up the rest of the cell is the continuous, enveloping phase, or *vice versa*. There are several proofs that the former is decidedly the case.

The chemistry of fat production in cells is such, first of all, that the fat is laid down in finely divided particles. When fat is newly synthesized in the cells from fatty acid and glycerin, the particles are originally of molecular dimensions only. If the molecules of fat are formed in a hydrated colloid (like the protoplasm of the normal cell) the fat particles must tend, evidently, to remain finely divided unless something happens to bring about their coalescence.

Second, the question of whether, upon mixing two immiscible liquids with each other, we shall get a subdivision of the first in the second or of the second in the first, is governed to a certain extent by the quantitative relationships existing between the two. Speaking generally, oil will tend to become the disperse phase if little of it is beaten into much water, while water will become the disperse phase if the quantitative relationships are reversed. On the basis of probability alone, therefore, it may be assumed in advance that amounts of fat up to the values discussed thus far (25 percent of the total weight of the moist tissue) will go to form the divided phase, while the hydrated colloids making up the rest of the cell will form the continuous, enveloping one.

For a third proof in this direction, we need but point to the behavior of the body fluids and tissues discussed thus far toward paper, to the feel, and toward admixture with an aqueous dispersion medium like water. Blood, lymph,

bile, saliva, skeletal muscle, heart muscle, kidney, spleen, fat-free pancreas, brain and even nerve, do not "oil" but simply "wet" a paper with which they are brought in contact. Neither do these materials impart an oily "feel" when rubbed between the fingers. Finally, all these fluids or tissues may be readily mixed into and with water. They may, therefore, all be washed off and out of containing vessels as readily as ordinary milk or egg yolk. Were the oil the external or enveloping phase none of these things would be possible.¹

If this simple logic is acquiesced in, it means further evidence (were such still needed²) proving *untenable the biological concept that the cell is surrounded by a plasma-film of fat or fat-like materials*. Were this concept correct, all unicellular organisms and all multicellular aggregates (like the tissues) for which such a belief is supposed to be valid should oil paper, feel oily and resist admixture with aqueous solutions as markedly as do the pure fats and lipoids themselves. This, obviously, they do not do.

¹ See page 89.

² See the reference under MARTIN H. FISCHER cited on page 61.

V. ON FATTY CHANGE (FATTY INFILTRATION
AND FATTY DEGENERATION).

V. ON FATTY CHANGE (FATTY INFILTRATION AND FATTY DEGENERATION).

1. HISTORICAL REMARKS.

THE problems of "fatty infiltration" and "fatty degeneration" have been much discussed since RUDOLPH VIRCHOW¹ first defined the terms in the middle of the last century. Under the first term, VIRCHOW understood the excessive deposition of fat in a cell; under the second, a change, pathological for the most part, whereby the cell substance itself was converted into fat. VIRCHOW's views rested for the most part upon theoretical conceptions and upon histological studies. Chemical support for them was found some twenty years later through the work of CARL VON VOIT.² In the seventies of the last century, this author detailed experiments which tended to lift from the realm of speculation into that of experimental fact the suggestion of VIRCHOW that the proteins of the cell, for example, might be changed into fat. In his studies of metabolism, VOIT believed he had figures at hand which showed that the protein consumed by an animal can be converted into and stored as fat. This belief, which held sway for many years, was made the subject of trenchant criticism by E. PFLÜGER³ and his co-workers, who, on the basis of new analyses and a recalculation of the figures of VOIT, showed these figures to be inadequate to support his contention. *At the present time it may safely be asserted that while the conversion of protein into fat in the higher animals still remains a theoretical possibility, no experiments exist which prove it; and all evidence, as it now stands, is entirely against it.*

The hypothesis of VIRCHOW, according to which the pro-

¹ RUDOLPH VIRCHOW: Virchow's Arch., **1**, 94 (1847).

² CARL VON VOIT: Zeitschr. f. Biol., **6**, 277 (1870); *ibid.*, **7**, 433 (1871).

³ E. PFLÜGER: Pflüger's Arch., **77**, 521 (1899).

tein of a cell may be converted into fat, has in these later years been gradually replaced by one which holds that in fatty degeneration an excessive amount of fat simply becomes deposited in the affected cells. The term "fatty degeneration" has, therefore, come to blend more and more with the older one of "fatty infiltration." For this view G. ROSENFELD¹ has been chief sponsor. ROSENFELD and others with him fed animals fat of a composition different from that of their own bodies and after having discovered that the foreign fat is laid down as such in the fat depots of the animals, these authors poisoned the animals with substances known to be capable of producing extensive fatty degeneration (phosphorus, chloroform, alcohol, phlorizin, etc.). On analyzing the fat found in the organs which had undergone the experimentally produced fatty degeneration, the authors discovered it to be identical with the foreign fat previously fed these animals. On the basis of these observations, ROSENFELD and those of his opinion hold that in fatty degeneration there merely occurs, for reasons as yet little understood, a transport and increased storage of the body fat in the affected cells. In further support of their views and against the idea that some constituent of the cell protoplasm itself (like the protein) is converted into fat, they adduce the fact that when poisons known to produce fatty degeneration are given to lean (fat-free) animals, fatty degeneration of the visceral organs is not obtained. Did the fat of fatty degeneration really come from the protoplasm of the cells themselves, then fatty degeneration should naturally be as easily obtainable in lean animals as in fat ones.

But further study of the subject has shown that in fatty degeneration this abnormally great infiltration with fat neither needs to occur, nor does occur. *Quantitative chemical analyses have gone to prove that even in heavily degenerated organs the amount of fat actually found in them need*

¹ G. ROSENFELD: *Ergebnisse d. Physiologie*, **1**, 1^{te} Abth. 651 (1902); *ibid.*, **2**, 1^{te} Abth. 50 (1903).

not exceed their normal fat content. In fact, many analyses are at hand which show that organs in fatty degeneration may contain *less fat than is normal* for them.¹

The concept of fatty degeneration is, therefore, seen to rest chiefly on purely histological (optical) grounds. It simply *looks* as though there were more fat in the affected cells. There exists no chemical proof showing that fat is produced from the cell protoplasm; the concept of an increased infiltration rests upon questionable evidence; and quantitative study shows that even such tissues as all pathologists will agree to be in a condition of fatty degeneration may contain no increase in amount of fat above the normal if, indeed, they do not show an actual loss. *The real question regarding fatty degeneration, therefore, comes to this: how does a given amount of fat, previously invisible in a cell, become readily visible?*

2. "FATTY DEGENERATION" IN EMULSIONS.

It will help toward a juster appraisalment of some of the evidence to be offered later if we first reproduce some photo-micrographs of tissues in typical, fatty degeneration. Sections of normal kidney, heart muscle or nerve do not betray the presence of fat in them, but when these tissues have suffered a "fatty degeneration" or a "fatty infiltration" (as judged on the ordinary basis of optical appearance), pictures like those shown in Figures 17, 18 and 19 are obtained.² As already emphasized, chemical analysis shows that the actual amounts of fat found in the organs under such circumstances need not exceed the normal values, and yet it is now readily visible in the form of gross globules in all these tissues.

¹ G. ROSENFELD: *Ergebn. d. Physiologie*, **2**, 1^{te} Abth. 66 (1903); also G. WALTER: *Virchow's Arch.*, **20**, 426 (1861); A. E. TAYLOR: *Jour. Exp. Med.*, **4**, 399 (1899); *Jour. Med. Research*, **9**, 59 (1903); A. ROSENTHAL: *Deut. Arch. f. klin. Med.*, **78**, 94 (1903).

² Figure 17 is from E. GIERKE: *Aschoff's Path. Anat.*, **1**, 322, Jena, 1909; Figures 18 and 19, from F. B. MALLORY: *Pathologic Histology*, 90 and 92, Philadelphia, 1914.

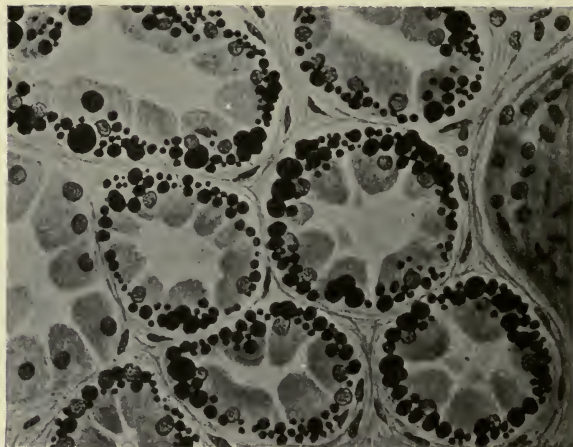


FIG. 17.

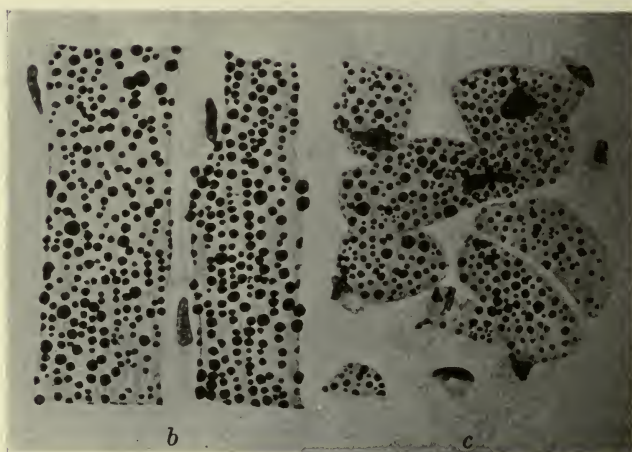


FIG. 18.

In keeping with our argument regarding the fat in cells, as thus far developed, we can only conclude that *fatty degeneration represents merely a coarsening of the normal fine emulsion of fat-in-protoplasm to a more readily visible size.*

In a previous section¹ it was pointed out that, depending

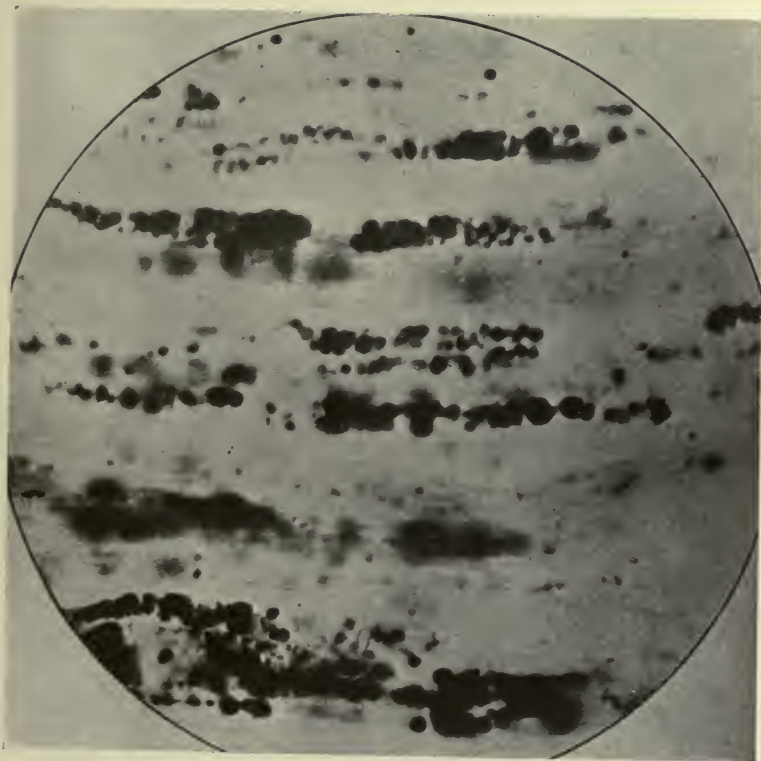


FIG. 19.

upon the nature of the hydrophilic colloid used to stabilize a fine emulsion of oil in an aqueous dispersion medium, different agencies capable of dehydrating the hydrophilic colloid may be used to bring about the separation of the constituents of the emulsion in grosser form. It behooves us now to ask what is the appearance of this separation

¹ See pages 47 to 51.



FIG. 20.

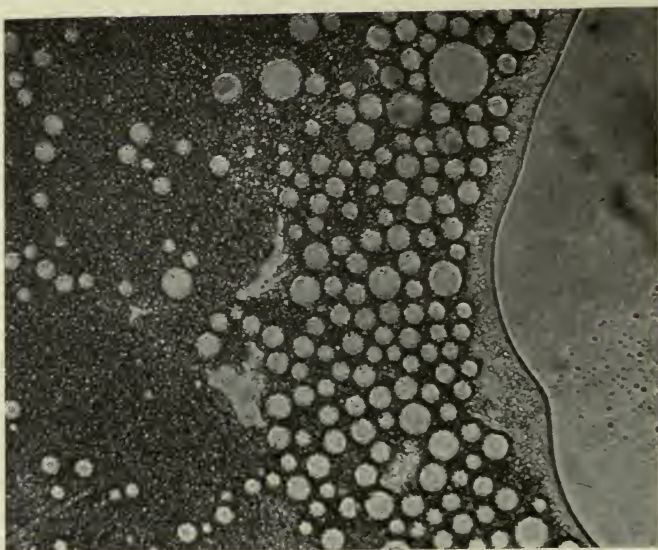


FIG. 21.

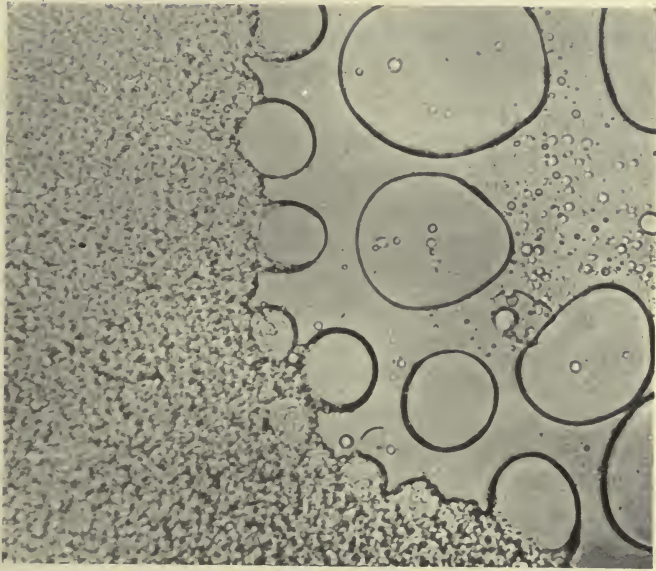


FIG. 22.

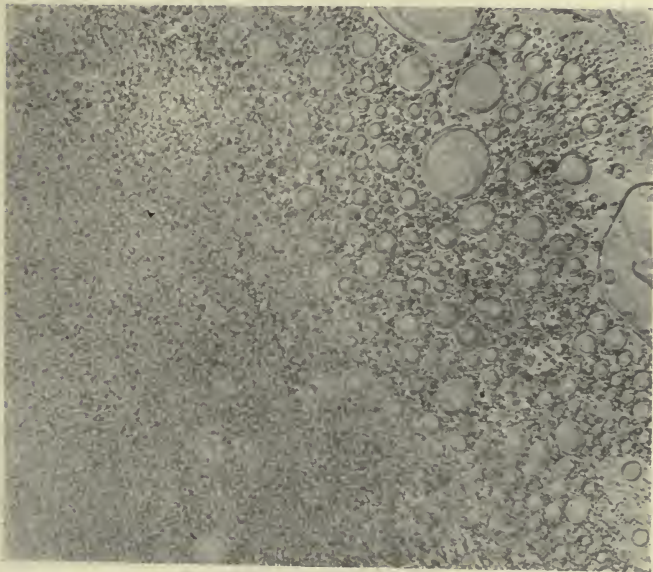


FIG. 23.

when followed microscopically. Figures 20, 21, 22 and 23 are introduced by way of illustration. Figure 20 is merely the microscopic picture (magnified some 850 times) of a rather fine emulsion of oil in soap. In Figure 21 is shown the effect of letting a drop of $\frac{1}{100}$ normal acid (hydrochloric, lactic, beta-hydroxy-butyric or diacetic) diffuse into the emulsion. As is clearly apparent, the destruction of the hydrophilic properties of the soap is followed by a coalescence of the oil droplets so that instead of being indistinguishable as before, they now become readily visible in coarse form. Figure 22 shows the same phenomenon, as produced by allowing a small amount of dilute alcohol to diffuse into the oil-in-soap emulsion. Figure 23 is introduced to show the effects of adding a little acid to an emulsion of oil stabilized in an alkali-protein (alkali-casein). Since neutral casein is less hydrophilic than the alkali-protein, the emulsion undergoes "fatty degeneration" as soon as the acid is added to it.

3. ANALOGY BETWEEN THE CHEMICAL CONDITIONS FAVORING FATTY DEGENERATION AND THOSE PRODUCING COARSENING IN EMULSIONS.

It should now be emphasized that there exists not only entire agreement between the *physical* phenomena characterizing the coarsening of an emulsion and fatty degeneration, but also between the *chemical* conditions governing the two.

Among the best established factors now recognized as active in the production of fatty degeneration, either experimentally or under clinical circumstances, are poisoning with phosphorus, lead or arsenic, anesthetizing with chloroform,¹ ether or alcohol, slow poisoning with acid, administration of phlorizin, the existence of diabetes, anemia² or

¹ See in this connection EVARTS A. GRAHAM: Jour. Exp. Med., **22**, 48 (1915).

² See THOMAS R. BOGGS and ROGER S. MORRIS: Jour. Exp. Med., **11**, 553 (1909).

general or local circulatory disturbances (thrombosis or embolism with infarction).

When it is recalled that hydrated proteins are of first importance for the stabilization of fat in protoplasm, it at once becomes apparent that several of the substances above enumerated are of a type to favor directly the dehydration of certain of the body proteins. Such substances may, therefore, be assumed to play a direct part in the initiation of "fatty degeneration" in living cells.

But phosphorus, the heavy metals and the anesthetics also interfere with the normal oxidation chemistry of the body cells. Such interference, as known since the classic studies of F. HOPPE-SEYLER, T. ARAKI,¹ H. ZILLESSEN,² etc., is followed by an abnormal production and accumulation of acids in the poisoned tissues. The effect of the acids upon protoplasm has been discussed many times before. They make certain of the cell proteins develop an increased capacity for holding water. When water is available, the involved cells will, in consequence, swell (become edematous).³ As the cells swell, the concentration of the protein in them is reduced, wherefore a tendency toward fatty degeneration develops for the same reason that a tendency to break increases in an emulsion, as the hydrophilic colloid stabilizing the finely divided oil is diluted.⁴

But the acids which thus increase the hydration capacity of certain cell proteins tend at the same time to *decrease* that of others. For instance, certain globulins, which in the normal cells and fluids of the body are united to alkali (as the alkali-casein of milk), possess in this form greater hydrophilic properties than when neutral.⁵ The addition of acid to cells containing proteins of this type tends, therefore, to

¹ T. ARAKI: Zeitschr. f. Physiol. Chem., **15**, 335 and 546 (1891); *ibid.* **19**, 422 (1894).

² H. ZILLESSEN: Zeitschr. f. Physiol. Chem., **15**, 387 (1891).

³ MARTIN H. FISCHER: *Edema and Nephritis*, 2nd edition, New York, 1915.

⁴ See pages 37 and 47.

⁵ See page 33.

dehydrate them. The swelling of the one set of proteins combined with the dehydration of a second yields what the pathologists call "cloudy swelling," as has been previously pointed out.¹ Through the dehydration of this second type of protein, the tendency of the involved cells to approximate pure water in composition is further increased, while the tendency of the protoplasm to hold apart the fat subdivided in it is correspondingly diminished. In other words, "fatty degeneration" is aided still more.

These facts will serve to explain what the pathologists have so often noted, namely, that "*cloudy swelling*" is both a precursor and an accompaniment of "*fatty degeneration*."

What has been said of acid intoxication and of the consequences incident to the poisoning of man or animals with the metals, with phosphorus or the anesthetics, holds also when such acid intoxication is secondary to direct carbohydrate starvation or the indirect starvation consequent upon phlorizin or pancreatic diabetes. It holds, too, for the abnormal production and accumulation of acid consequent upon an inadequate oxygen supply, or such as is incident to general or local circulatory disturbances following heart disease, vascular disease, thrombosis or embolism.

4. TISSUE RIGIDITY AND TISSUE "SOFTENING."

We should like next to call attention to the help which the colloid-chemical study of emulsions yields toward understanding the so-called "softening" of organs suffering from "fatty degeneration." As illustrated particularly well in infarctions of the kidney or brain, or in the after-effects of nerve section (WALLER'S degeneration), the involved areas after an initial swelling with graying (cloudy swelling) accompanied, or followed, by a yellowing (fatty degeneration), tend to soften, to shrink and to liquefy. What

¹ See MARTIN H. FISCHER: *Kolloid-Zeitschrift*, 8, 159 (1911); also *Oedema and Nephritis*, 2nd edition, 455, New York, 1915, where references to the older literature may be found.

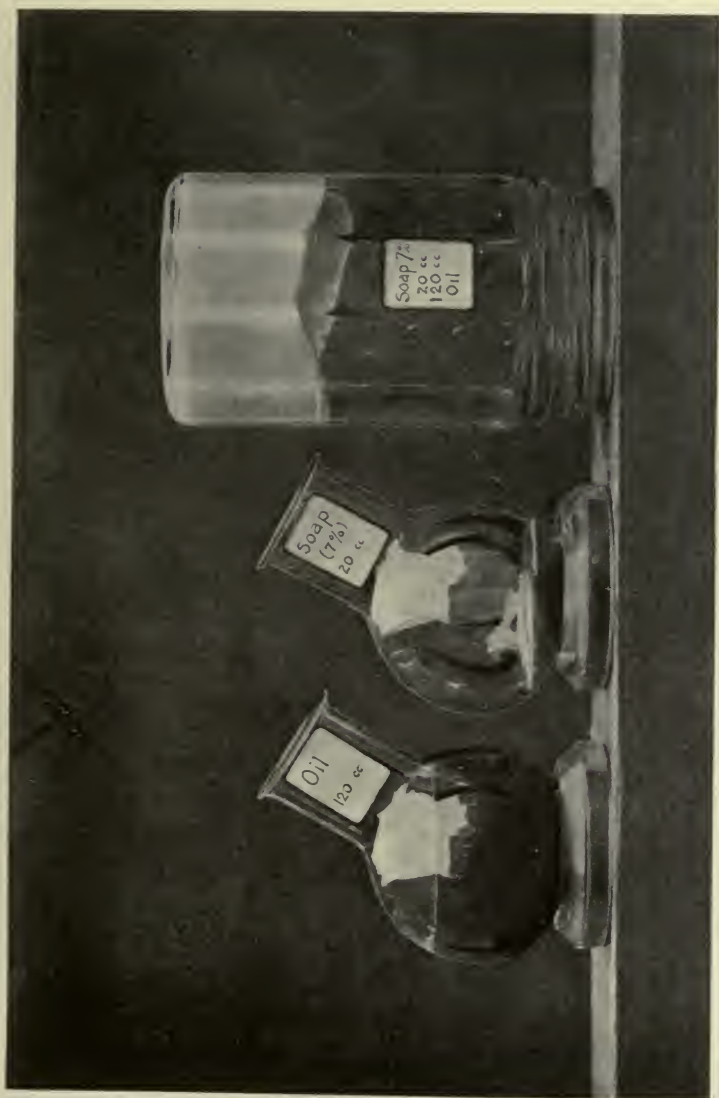


FIG. 24.

is the reason for this softening after the initial increase in firmness due to the swelling?

§1.

As has several times been noted by different authors, there occurs a marked increase in viscosity whenever an oil is emulsified in such an aqueous dispersion medium as a hydrated soap or a hydrated protein solution. We have touched upon this fact before.¹ Figure 24 will perhaps illustrate the matter better than many words. In the two flasks are contained, respectively, 120 cc. of cottonseed oil and 20 cc. of a 7 percent potassium-soap solution. The two are labile liquids. But let the oil be emulsified in the soap and the result-



FIG. 25.

ing mixture becomes so stiff that the mixing vessel containing it may be turned upside down without its flowing out. The same great viscosity of an emulsion is shown in Figure 25. This is the picture of an emulsion of 300 cc. of oil in 25 cc. of 25 percent potassium-soap.

Let us next observe what happens when this stiff oil-in-soap emulsion is broken by any means whatsoever, as through simple drying, the addition of a little acid or alcohol, or admixture with a properly chosen salt. As the emulsion breaks, there is a fall in vis-



FIG. 26.

¹ See page 40.

cosity back to that of the individual constituents of the emulsion. While a metal rod is held in any given position in the viscid emulsion of Figure 25, it falls to the edge of the container as soon as the emulsion is broken, as shown in Figure 26.

Much of the normal viscosity or rigidity of the tissues is due to their emulsion character. The "softening" of the organs as observed in various pathological states is due to a breaking of this emulsion.

§2.

Some corollaries of this simple conclusion are of biological interest. It should first be emphasized that emulsions are, by definition, diphasic or polyphasic systems of mutually immiscible liquids. Oil-in-hydrated protein, oil-in-hydrated soap, etc., are, therefore, not the *only* emulsions to be thought of in the case of protoplasm. *We may have also emulsions of one kind of hydrated protein in a second, or of hydrated carbohydrates in hydrated protein, etc.* So even in the absence of fat (which substance is to be thought of particularly in such fat-rich organs as the peripheral nerves and the central nervous system) we may obtain highly viscid complexes from emulsification in each other of what are, to begin with, mobile liquids.¹ We find in these considerations *an explanation of those properties of protoplasm which have inclined us to think of it, on the one hand, as "solid," on the other, as "liquid."* Elasticity and maintenance of form argue for the solid nature of protoplasm; that it shows surface tension phenomena, that it allows materials to diffuse into and through it, and that it acts chemically as though it were liquid, argue for its fluid character. The emulsion character of protoplasm explains why the two may be associated as they are. Being composed for the most part of phases which are by themselves liquid, there exists no *a priori* reason why the essential

¹ These systems are now being studied in our laboratory and will be reported upon later.

properties of the liquids should be lost when they are mixed into each other. But, if the liquids are mutually insoluble (practically), emulsions are formed; and as this happens, the

viscosity of the mixture rises until the properties of solids are approximated.

§3.

It behooves us, in connection with certain findings characteristic of tissue softening (as observed in the brain, for example), to study a little more closely the changes observable in a breaking or a broken oil emulsion. In Figure 27 is shown an oil-in-soap emulsion which has been broken through mere dilution with water (which not only dilutes the soap to below the concentration necessary for the maintenance of the emulsion but destroys its hydrophilic characteristics, since the soap goes into "true" solution in much water). At the top of the liquid column is seen a layer of pure oil (a).

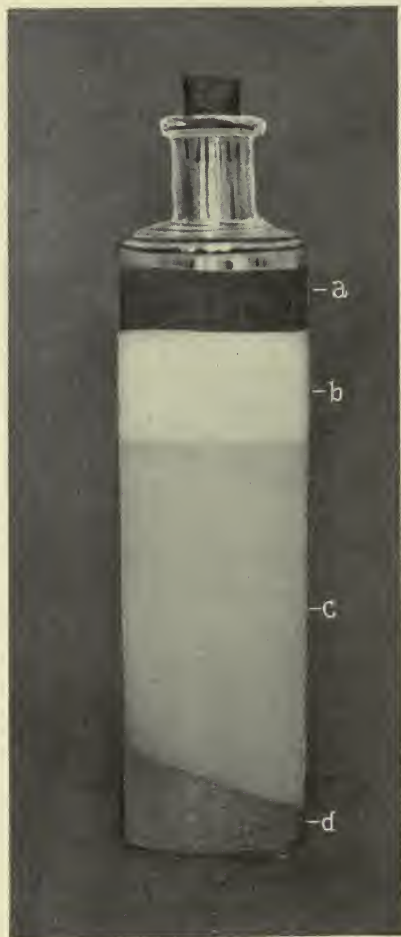


FIG. 27.

The white collar below this (b) is an emulsion of soap-water in oil. Next (c) comes an emulsion of oil in soap-water, and lowest in the bottle is (practically) pure soap-water (d). When studied microscopically the pure oil shows nothing;

the dark spots in Figure 28 are dust particles that indicate that the oil layer is really in focus. In Figure 29 is shown the appearance of the white collar; the globules are soap-water emulsified in the oil. Figure 30 is practically indistinguishable from Figure 29, but it represents the opposite type of emulsion, namely, one of oil in soap-water. Figure 31 is taken from the bottom of the tube. A few scattered globules of (colloidally) divided oil in the process of Brownian movement may be seen; the field is, in other words, practically pure soap-water.

Pathological examination of the material from a well-softened area (as from the brain) shows this to consist of the same types of materials. There are found large globules of clear oil, oil with water emulsified in it, water with oil emulsified in it, and water. The four materials are not, of course, as pure as here indicated. Dissolved and precipitated protein, for example, is likely to contaminate any of the phases, just as the particles of dissolved or precipitated protein or soap contaminate the different divisions of an emulsion prepared and broken under laboratory conditions.

5. FURTHER HISTORICAL REMARKS.

With our concept in mind that fatty degeneration represents merely a coarsening of the normal fat-in-protoplasm emulsion, under circumstances and through agencies which lead to the dilution and dehydration of the hydrophilic colloids which normally keep the fat apart in finely divided form, we need now to take a look backward at the wealth of experimental and literary material available on the subject of fatty degeneration, in order to emphasize the value of certain older researches.

Of first interest in this direction are the studies of HAUSER,¹ and F. KRAUS² who found that organs removed from the body and kept under sterile conditions gradually un-

¹ HAUSER: Arch. f. exp. Path. u. Pharm., **20**, 162 (1885).

² F. KRAUS: Arch. f. exp. Path. u. Pharm., **22**, 174 (1887).



FIG. 28.

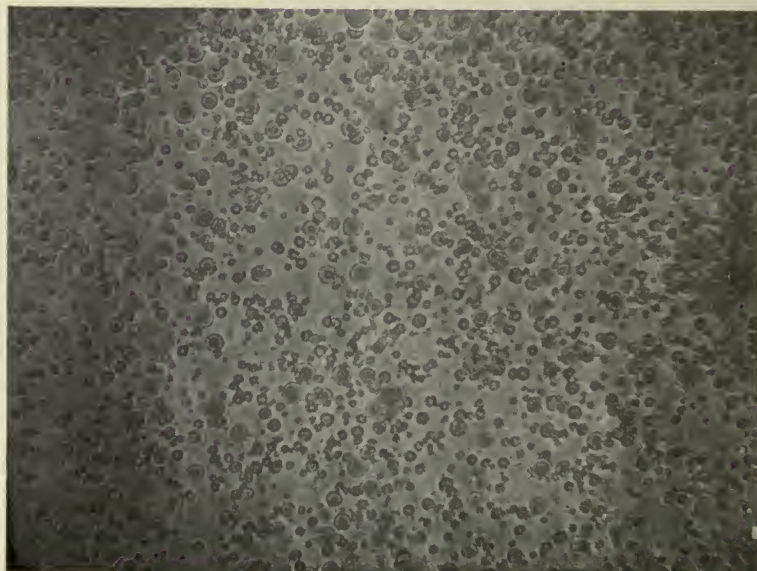


FIG. 29.

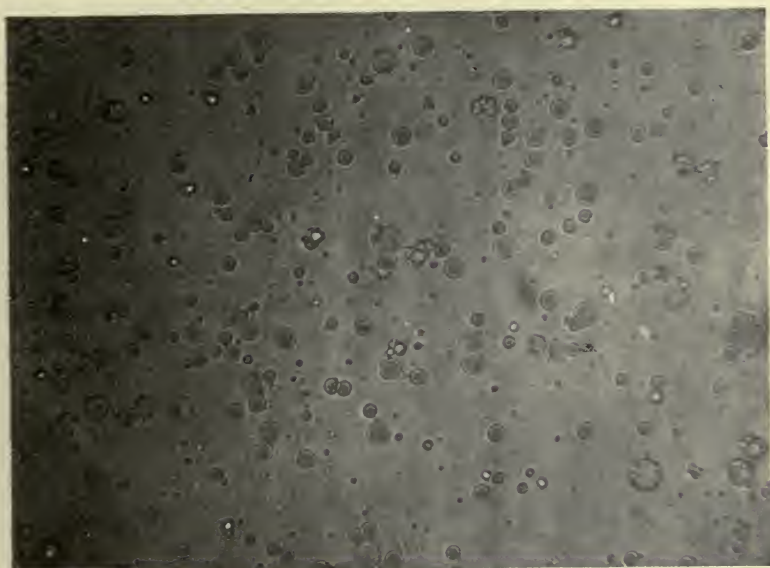


FIG. 30.



FIG. 31.

dergo a "fatty degeneration." Similar observations have been made since by F. SIEGERT,¹ A. ORGLER,² WALDVOGEL³ and others. Several of these authors have used this post mortem appearance of fatty degeneration as an effective argument against the view that fatty degeneration either needs to be, or is, preceded by a "fatty infiltration" of the involved tissues. In all of these experiments there is, of course, no possibility of getting an increased infiltration of fat, and in many of them even the possibilities of an increased fat production post mortem from some constituent of the cell protoplasm are not at hand.

We should ourselves interpret these findings by saying that the normal fat content of these organs simply becomes more easily visible with the changes consequent upon their removal from the body. We do not even think it necessary to call upon complicated enzymatic processes to explain why the fatty change must occur post mortem. As soon as organs of warm-blooded animals are deprived of their circulation, they begin to develop lactic and other acids which in these "dead" organs act in the manner described above when discussing the fatty degeneration of living tissues. The acids bring about a dilution and a dehydration of various body colloids and so the finely divided fat, originally held apart, runs together into larger globules.

In connection with the question of the chemical conditions which thus make it possible for the fat found normally in the cells to flow together into larger droplets, the observations of V. RUBOW⁴ are of much interest. RUBOW holds that normally fat is dissolved in the body fluids and cell protoplasm and hence is invisible. This "dissolved" state of the fat is maintained through the presence of alkali in these fluids and cells. If the amount of alkali is diminished, either through an increased production or a decreased re-

¹ F. SIEGERT: Hofmeister's Beiträge, **1**, 114 (1901).

² A. ORGLER: Virchow's Arch., **176**, 413 (1904).

³ WALDVOGEL: Zentralbl. f. Stoffwechsel u. Verdauungskr., **4**, 405 (1903); Virchow's Arch., **177**, 1 (1904); Zeitschr. f. physiol. Chem., **42**, 200 (1904).

⁴ V. RUBOW: Arch. f. exp. Path. u. Pharm., **52**, 173 (1905).

removal of acids from the tissues, RUBOW thinks that the solubility of the fat is thereby decreased, wherefore it separates out in coarse form. The views of RUBOW have found little acceptance because to keep the fat "dissolved," enough alkali must be present to convert the fat into soap, and chemical analysis shows that the tissues richest in fat contain no amount of alkali adequate for such purpose. The fat of the cells is, moreover, neutral fat and not soap. But in pointing out that many of the best known methods of producing fatty degeneration are such as lead to an increased production or accumulation of acids in the involved cells, and in emphasizing this as an important factor in the production of fatty degeneration, he has made a fundamental contribution to the subject. The acids do not make a previously soluble fat insoluble, but, as indicated above, these, and similar agencies, through the destruction of hydrophilic colloids, favor the coalescence of finely divided and therefore invisible droplets of fat into larger, more readily visible droplets.

The view that in "fatty degeneration" the fat which becomes visible in the cell is derived from a precursor of some sort, like lecithin, we need not discuss. Carefully made quantitative chemical analyses now show, on the one hand, that even in the most extreme cases of "fatty degeneration" no decrease may be observable in the lecithin content normal for the involved cell, while, on the other hand, amounts of fat are found in certain cells that have undergone "fatty degeneration" which exceed enormously any that could have been produced from the amounts of lecithin found in the cell.

VI. THE ADIPOSE TISSUES AND THE FATTY
SECRETIONS.

VI. THE ADIPOSE TISSUES AND THE FATTY SECRETIONS.

THUS far we have discussed the problem of fat in cells and secretions only under circumstances in which the amount of the fat has remained relatively low. Even figures alleged to be anormally high (such, for example, as are encountered in tissues with fatty degeneration or fatty infiltration) do not run above some forty percent of the moist weight of the organ. PERLS¹ observed this value in fatty infiltration of the liver of a chronic alcoholic.

To get fat values in cells or secretions which exceed forty percent, we need again to pass into the physiological realm.

1. THE FATTY TISSUES.

According to GORUP-BESANEZ,² human bone marrow contains 96.0 percent of fat, and adipose tissue contains 82.7 percent. Table V gives another analysis of human adipose tissue, as well as several of fats from animal sources.

TABLE V.
COMPOSITION OF VARIOUS ADIPOSE TISSUES.

	Fat.	Water.	Protein.
Human fat ¹	82.5	15.0	2.5
Pig fat ²	81.9	7.9	1.8
Bacon ²	64.0	18.8	9.6
Suet ³	77.7	13.7	4.6

¹ VOLKMANN: Vierordt's Daten und Tabellen, 190, Jena, 1888.

² ATWATER and BRYANT: Quoted by GRAHAM LUSK, Science of Nutrition, 2nd edition, 366, Philadelphia, 1909.

³ ATWATER and BRYANT: *l. c.* 366.

The features of interest in connection with this table

¹ PERLS: Cited by J. GEORGE ADAMI, Principles of Pathology, 1, 821, Philadelphia, 1908.

² GORUP-BESANEZ: Quoted by W. D. HALLIBURTON, Schäfer's Text-Book of Physiology, 1, 17, Edinburgh, 1898.

are not only the high percentages of fat but the high percentages of water found in the tissues named. Let it be noted that some seven to fifteen percent of water is constantly encountered in all such tissues. Why are these amounts so constant, and how is the water carried in the fat tissues? As readily apparent, the figures lie in all cases beyond the simple "solubility" limits of water in fat.

The adipose tissues, too, are emulsions, but of the type of water-in-fat (hydrated colloid-in-fat). The proofs for this contention are several. First, the high proportion of the fat in the total bulk constituting the fatty tissues takes the mixture to or beyond the "breaking" point of the oil-in-hydrated colloid type of emulsion. Second, the fatty tissues impart a greasy "feel" when rubbed between the fingers, and "oil" a paper placed in contact with them. But the best proof is perhaps furnished by direct microscopic examination of thin shavings or crush preparations of the fatty tissues themselves. When tiny fragments of adipose tissue are removed from the central portions of the fat depots of different animals and examined microscopically, pictures like those shown in Figures 32, 33 and 34 are obtained. Figure 32 is fresh pig's fat. The hydrated colloid-in-oil type of emulsion is not destroyed even through subjection to the processes of salting and smoking by which such fresh pig's fat is converted into the bacon shown in Figure 33. Figure 34 presents the appearance of fresh rabbit's fat.

It will be noted that the fats found in all these adipose tissues have rather low melting points. In adipose tissues containing high melting point fats (like beef suet) the drop-let character of the aqueous phase in the fat is less apparent. This is because the water is crushed out of shape between the palmitin, stearin and other high melting point fats which constitute the bulk of these tissues. Actual crystallization of the bulk of these fats is readily observable, especially in the cold. When the tissues are kept at body temperature, or above, the liquid droplets making up the aqueous phase become readily visible.

What has been said of the adipose tissues of animals holds also for the solid tissues of plants which are high in fat. An illustrative series of analyses showing the composition of nuts is given in Table VI.¹ Composition, microscopic analysis, and reaction to feel and paper again prove that *whenever the proportion of fat runs high, the nut consists essentially of an emulsion of water (hydrated colloid) in fat.* Of the nuts listed in Table VI, those standing highest in the list are those which in their natural state are most likely to be greasy, while those lowest in the list are more commonly mealy. In any nut, mere drying incident to ageing increases its greasiness, while this change is often hastened for culinary reasons by oven drying or roasting the nuts.

TABLE VI.
COMPOSITION OF NUTS.

Nut.	Fat.	Water.	Protein.	Carbohy- drate.	Ash.
Hickory.....	60.7	3.7	13.1	10.3	1.6
Filbert.....	58.8	3.7	13.3	11.7	1.8
Butternut.....	55.1	4.4	23.7	3.2	2.2
Almond.....	49.4	4.8	17.8	15.6	1.5
Cocoanut.....	45.5	14.1	4.8	25.1	1.3
Peanut.....	34.7	9.2	21.9	22.0	1.5
Chestnut.....	4.9	45.0	5.3	37.9	1.0

2. THE FATTY SECRETIONS.

Just as the adipose tissues are seen to be emulsions of hydrated colloid-in-fat, so are the fatty secretions. How the fatty secretions come to be formed from animal or vegetable protoplasm (which, except in the case of the essentially adipose tissues, represents an emulsion of fat-in-hydrated colloid) is well illustrated in the phenomena accompanying the change of milk into butter.

Whole milk represents, as universally known, an emulsion of oil in a diluted set of hydrophilic colloids. During

¹ ATWATER and BRYANT: Quoted by GRAHAM LUSK, *Science of Nutrition*, 2nd ed., 374, Philadelphia, 1909.

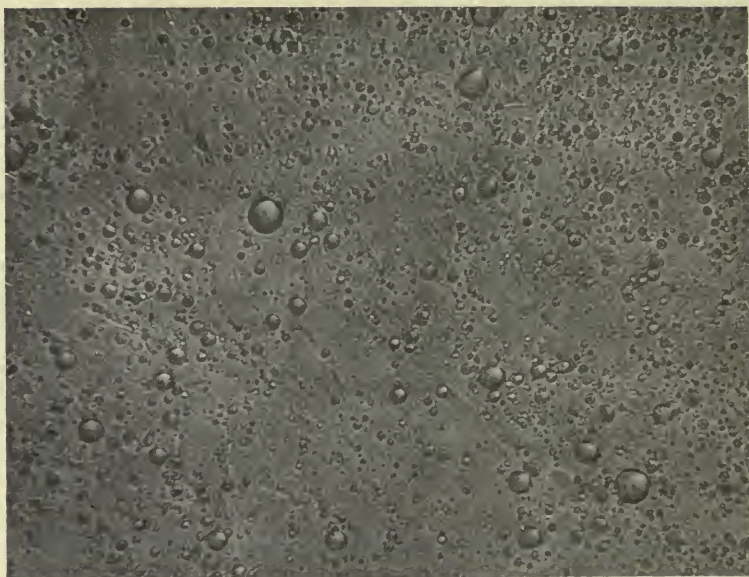


FIG. 32.

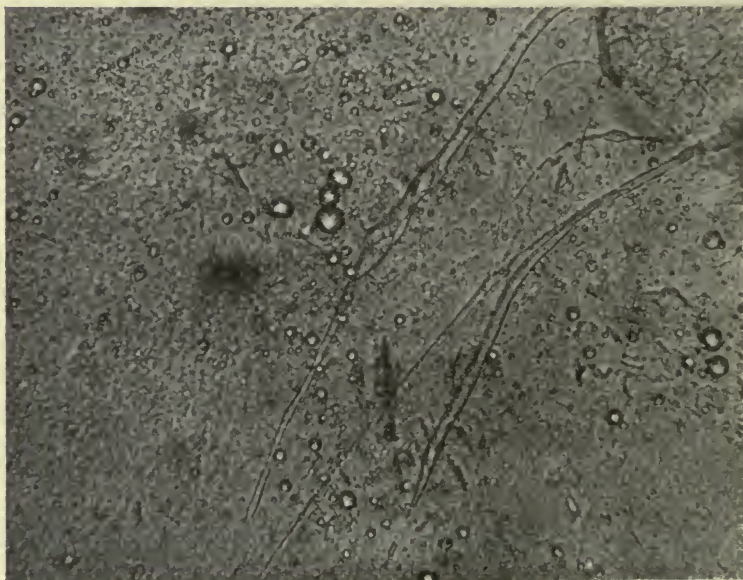


FIG. 33.

the lactation period, the secretory cells of the mammary glands grow rapidly, they become highly charged with fat, the fat coalesces into readily visible particles (fatty degeneration) and finally the gradually swelling cells burst to yield the fat-in-hydrated colloid emulsion which is called milk. Whole, unchanged milk shows little tendency to form butter. The tendency to do so is increased, first, by

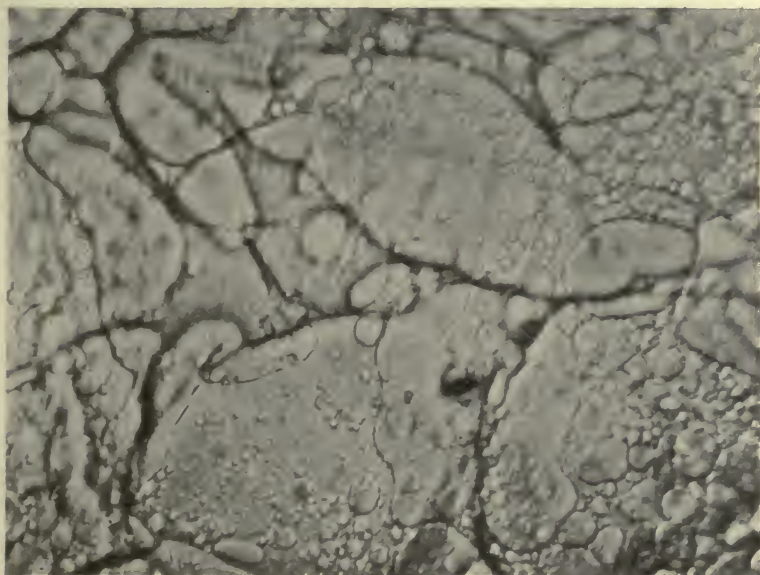


FIG. 34.

allowing the fat particles in the unit volume of hydrated colloid to concentrate (through letting the cream rise or by mechanical separation of the cream), and second, by aiding the dehydration of the colloids to which the water is so largely bound, as by allowing the cream to sour. Since the hydrated colloids tend to collect in the surface layers between the fat particles and the aqueous phase of the cream, efforts are made to break these layers, and so to hasten coalescence of the fat droplets, by churning. *The combined efforts therefore bring about a progressive increase in the concentration of the oil with a decrease in the concentration*

of the hydrated colloid until the instability of the oil-in-hydrated colloid emulsion becomes so great as to "break" and yield the hydrated colloid-in-fat emulsion which we call butter.

This concept may be tested in various ways. Milk and cream "wet" paper, are not greasy to the touch and microscopically show particles of oil divided in a continuous aqueous phase.

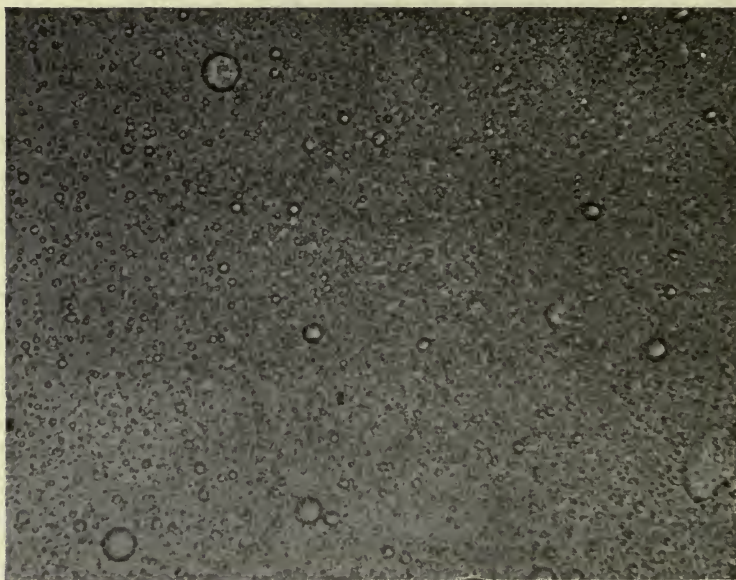


FIG. 35.

Butter, on the other hand, "oils" paper, feels greasy, and microscopically is seen to consist of an emulsion in which the aqueous phase (hydrated colloid) is finely divided in droplet form in the continuous oil phase.

Table VII¹ illustrates the changes in chemical composition which milk shows in its progress toward butter. To the table has been added an analysis of oleomargarin which not only chemically stands close to true butter, but which, as shown in Figure 35, is quite like it in its physical aspects

¹ ATWATER and BRYANT: Quoted by GRAHAM LUSK, *Science of Nutrition*, 2nd ed., 370, Philadelphia, 1909.

also. It is, in fact, really an emulsion of hydrated colloid-in-fat.

TABLE VII.
COMPOSITION OF DAIRY PRODUCTS AND OLEOMARGARIN.

	Fat.	Water.	Protein.
Whole milk.....	3.8	87	3.2
Cream.....	17.6	74	2.4
Butter.....	80.8	11	1.0
Oleomargarin.....	78.9	9.5	1.2

The formation of the fatty secretions by animals or plants represents a change from an oil-in-aqueous phase type of emulsion to an aqueous phase-in-oil type, which is entirely analogous to the change of milk into butter. Under natural conditions, this change is produced by drying alone.

In illustration of what happens in the formation of the fatty secretions, we may study the behavior of ear wax. Its chemical composition is indicated in Table VIII, taken from PETREQUIN and CHEVALIER.¹

TABLE VIII.
PERCENTAGE COMPOSITION OF EAR WAX.

	Fat.	Water.	Potassium Soap.	Other Organic Materials.	Ash.
From adults.....	26	10	52	12	Traces
From the aged.....	30.5	11.5	41	17	

The most striking features in these analyses are the characteristic, rather high, water percentages, the enormous (colloid) soap values and the rather high fat contents. In other words, ear wax is a mixture of hydrated soap and fat. Coming as it does from a set of sebaceous glands, the protoplasm of which, to begin with, represents an emulsion of oil-in-hydrated colloid, the greasy feel of ear wax and its

¹ PETREQUIN and CHEVALIER: Quoted by F. HOPPE-SEYLER, *Physiologische Chemie*, 704, Berlin, 1881.

oily properties already indicate that in the process of secretion and in the process of drying after secretion, a change must have occurred to the hydrated colloid-in-oil type of emulsion. Microscopic examination bears this out. In Figure 36 is shown some *moist* ear wax. The droplets of hydrated colloid are readily apparent. As the ear wax dries more perfectly, the soap which constitutes the bulk of the hydrated colloid in the oil tends to become more flaky or crystalline. The droplets, therefore, largely vanish and the appearance shown in Figure 37 ensues. This is microscopically similar to that shown by any hydrated soap-oil mixture in which, through evaporation, an emulsion of the type of aqueous phase-in-oil has become established. Figure 38 is a photo-micrograph of such a hydrated soap-in-oil emulsion produced through gradual evaporation of the water from what was originally an oil-in-hydrated soap emulsion. The clear streak in the middle of the field is pure oil; on each side of it is seen a hydrated soap-in-oil emulsion.

In order not to lengthen our discussion unduly, let it simply be noted that what was said here regarding ear wax holds also for sebum, smegma and vernix caseosa. It holds also for the fatty secretions encountered pathologically in cysts, tumors, etc., and similarly for the oily, fatty and resinous secretions given off by different plants.

3. OPTICAL CHANGES INCIDENT TO PHYSICAL CHANGES IN EMULSIONS.

Much interest is attached to the gross changes which accompany the transformation of an oil-in-hydrated colloid emulsion into one of a hydrated colloid-in-oil type. As already emphasized, simple drying leads to this transformation in many oil-in-hydrated colloid mixtures. An illustrative example is offered in the drying of an oil-in-hydrated soap emulsion. When a stiff emulsion of this type is smeared as a rather thick layer over the surface of a cylinder, as shown in Figure 39 the water gradually evaporates. Dur-



FIG. 36.

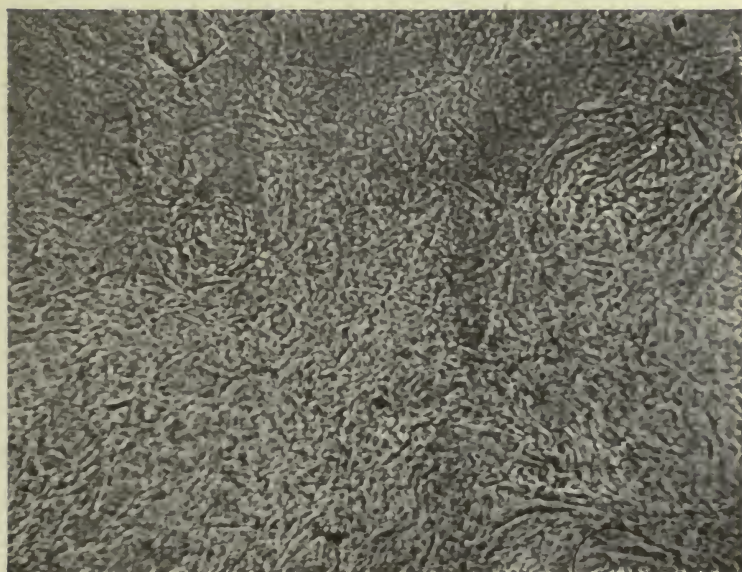


FIG. 37.

ing this evaporation it is first to be observed that the mixture, which originally was intensely white, becomes translucent and finally so transparent that printing may be read through it. If the drying is continued beyond this point, beads of oil appear upon the surface of the emulsion, which gradually increase in size, coalesce and drip to the

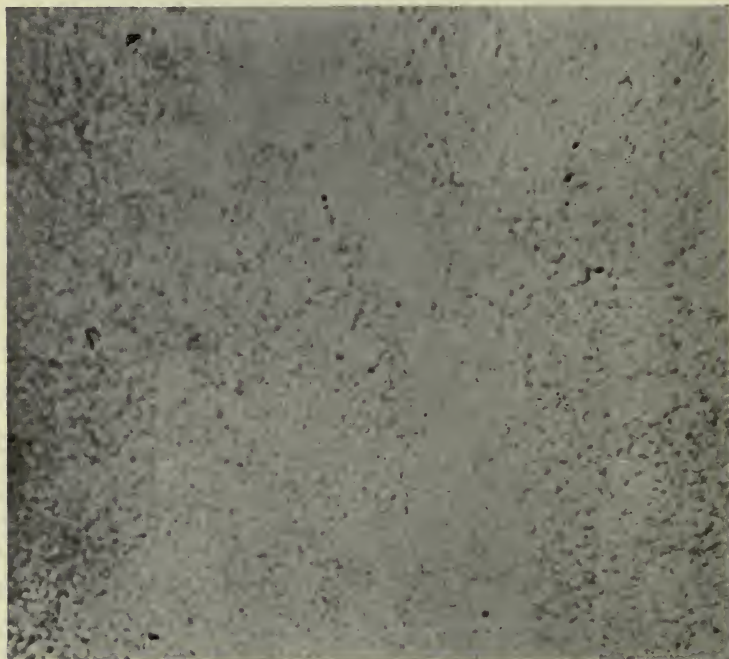


FIG. 38.

bottom. The horizontal layer in the bottom of the cylinder in Figure 39 is pure oil that has collected in this way.

The formation of such oil beads occurs also in drying oil-in-hydrated protein emulsions. An illustration of this process is seen in Figure 40 which is a slightly enlarged photograph of a gradually drying mass of egg yolk.

The gradual change from opaque whiteness to translucency and final transparency with drying of the emulsion is illustrated further in Figure 41. Over *a* in the picture is

shown a glass plate freshly smeared with an oil-in-hydrated colloid (soap or protein) emulsion. The design placed behind this plate cannot be seen. Over *b* in the photograph is shown a similar smear made some hours earlier and from which the water has been allowed to evaporate; this plate has become so transparent that the design is readily visible through it.

This gradual increase in transparency may also be observed microscopically as shown in the case of a coarse oil-in-soap emulsion in Figure 42. The field marked *b* is from the drying edge of the microscopic specimen; the light passes through this portion of the field with less refraction than through the remaining portion *a* included in the photomicrograph.



FIG. 39.



FIG. 40.

The behavior of drying oil-in-hydrated colloid emulsions is analogous to various biological processes. The experi-

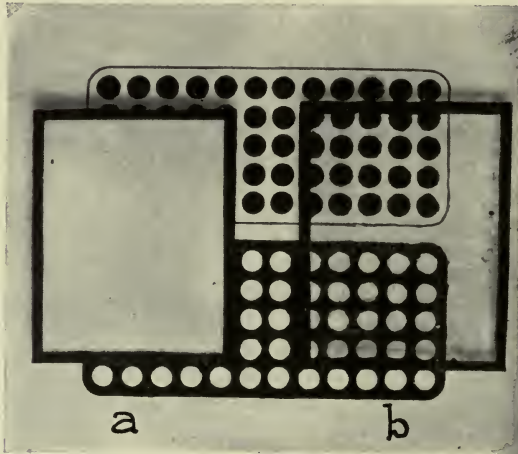


FIG. 41.

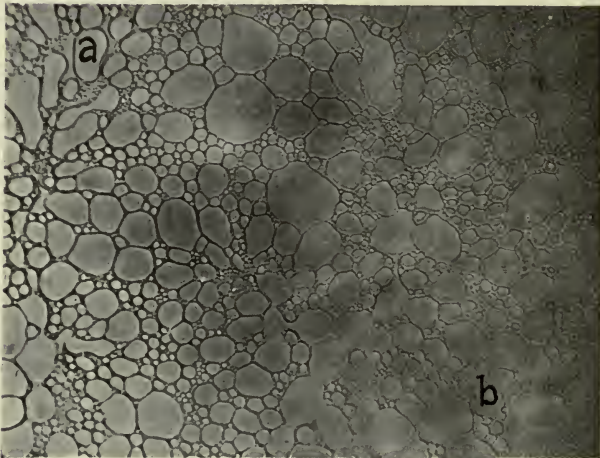


FIG. 42.

ments on emulsions show how such dehydration effects as are incident to simple drying lead up to and permit the separation of the fat phase in almost pure form — a process analogous to the secretion of almost pure fat by various

animal or plant cells. Second, the clearing of such diphasic systems explains how tissues, originally opaque, may become entirely transparent. Tissues composed of oil-in-hydrated protein, or of hydrated protein in a second hydrated protein, for example, and originally opaque, may through simple changes in the water content of the one phase permit the indices of refraction of the two phases to come so close together that they become entirely transparent. It is to considerations of this kind that we must turn, we think, when we attempt to understand how the formation is made possible of such clear tissues as compose the cornea, Wharton's jelly of the umbilical cord, the hyalin structures constituting cartilage, etc., from the opaque structures which were their antecedents.

VII. ON THE NATURAL AND ARTIFICIAL
PRODUCTION OF MILK.

VII. ON THE NATURAL AND ARTIFICIAL PRODUCTION OF MILK.

1. INTRODUCTION.

FROM what has been said in the previous sections, it is apparent that the ordinary cell is an emulsion of a fraction to several percent of fat and lipoids in a hydrated colloid. We followed in the last section the consequences of increasing the percentage of the fat in such a system. When, either through an increased laying down of fat in a cell or through simple loss of the water from a cell, we increase the concentration of the fat to beyond a certain critical point, a transformation of the original oil-in-water type of emulsion to one of the water-in-oil type takes place; in other words, either adipose tissue or a fatty secretion is formed, depending upon whether the oil concentration or water loss occurs within the tissues themselves or upon the surface of an animal or plant.

Let us now look at the results of the opposite type of change. *What happens if, instead of decreasing the amount of water in the ordinary fat-in-hydrated colloid which constitutes our cells, we increase it? Under these circumstances "milk" is produced.*

2. THE NORMAL (BIOLOGICAL) PRODUCTION OF MILK.

This is, first of all, the method which nature uses in the production of milk. As histological study shows, the alveoli of an active mammary gland consist originally of a single layer of nearly cubical gland cells. In the process toward milk production, these cells increase in length, pushing out toward the lumen of the alveolus. The portions farthest from the basement membrane to which these cells are attached (farthest, we would prefer to say, from the capil-

laries which supply oxygen to the gland cells) begin to show the appearance of fatty droplets in them. When morphological pathologists describe the process, they say that the peripheral portions of the secreting cell undergo "fatty degeneration." The facts are that the distal portion is swollen, often granular ("cloudy swelling") and studded with fatty granules. These peripheral portions of the cell finally swell so much that they "go into solution" and thus form "milk." The portion of the cell which remains and is attached to the basement membrane is then again cubical and again begins the series of changes just described.

Expressed in the terms of emulsion chemistry, this set of cellular changes represents the original emulsion of fat in the concentrated hydrophilic colloid (corresponding to the original cubical cell) becoming richer in water. One of the colloids in the cell swells while a second is precipitated. Together, this yields the "cloudy swelling" which, however, in the terms of emulsion chemistry means not only a decrease in the concentration of the hydrophilic colloids of an emulsion but a decreased capacity for holding water on the part of some of them. The tiny fat droplets of the original emulsion therefore tend to run together, to form larger ones which begin to appear in the distal portions of the cell (fatty degeneration). When this coarsened emulsion is still further diluted, when, in other words, the cells swell to the "solution" point, there results an emulsion of fat droplets in a dilute mixture of proteins (albumins and globulins) to which we are in the habit of attaching the name "milk." What happens is illustrated in Figure 43. When such a concentrated emulsion of oil-in-soap as is shown in the first jar in Figure 6 or of oil-in-protein as is shown in Figure 7 is merely diluted, the "milks" shown in Figure 43 result. These milks are readily miscible with all amounts of water, have the texture of the natural milks, readily wash out of their containers, do not feel greasy and, on standing, give rise to such a cream layer as is shown in Figure 44.

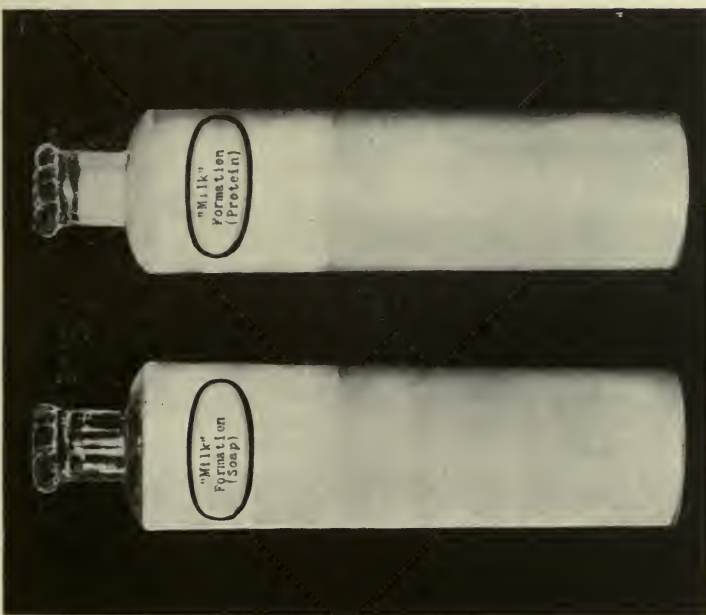


FIG. 43.



FIG. 44.

3. THE ARTIFICIAL PRODUCTION OF MILK.

As a matter of fact, we can not only mimic nature and test out the correctness of these deductions by repeating the whole series of changes under laboratory conditions, but in so doing discover laboratory methods of making milk artificially and of a type and composition which imitates perfectly, not only cow's milk but any milk for which we may have the necessary chemical constituents. Or we may thus "synthesize" milks which within wide limits may have any composition we may choose to give them.

A "synthesis" of milk has, independently of us, been accomplished by A. W. BOSWORTH.¹ BOSWORTH approached the problem from a chemical point of view. After first obtaining in pure form the characteristic fats, salts, carbohydrates and proteins of milk, he mixed them together again with the necessary water to yield the artificial milk he desired. Then, by working at temperatures which would make the fat fluid and by running the whole through a homogenizer, he produced the emulsion necessary to imitate natural milk from a physical point of view. BOSWORTH has carried out successful feeding experiments on infants with milks thus prepared.

BOSWORTH informed us that his method was beset with certain difficulties which were finally overcome. It proved not always easy to get the fat properly emulsified. What has been said in these pages regarding the mechanical and concentration conditions which must be met in order to prepare emulsions successfully, contains, we think, the answer to his difficulties. His method of producing an emulsion by homogenizing his fat in much water cannot yield as good results as when what may be termed the more "natural" method is followed of first dividing the fat into a rather highly concentrated hydrated colloid and then diluting the resulting mixture.

¹ A. W. BOSWORTH: Personal Communication, April, 1916.

In our own method of making artificial milk, we begin with the hydratable colloids that are to appear in the finished product. If cow's milk is to be imitated, we start with pure (amphoteric) cow's casein to which enough alkali is added to produce neutralization of the protein and only just enough water to furnish the optimum concentration for the division of the fat in it. For pure casein, with pure sodium carbonate as the alkali, and with distilled water, this point is reached when each gram of protein has 0.4 cc. molar sodium carbonate added to it; but the presence of other proteins, of other salts, etc., in the mixture at once changes this relation of the different elements to each other, and so the new optimum point must be discovered for each new mixture. The best guide as to when the right point is reached is



FIG. 45.

found in the peculiar crackling noise, so often noted by workers on the emulsions, produced whenever the hydration of the protein has been carried to the right point. The danger of getting poor results is greater when too much water is added than when the opposite is done. Once a concentrated emulsion of fat in hydrated casein has

been produced, it is an easy matter to dilute it, to add other proteins (like lact-albumin and lact-globulin) and finally the salts and the milk sugar to obtain the emulsion which will ultimately have all the physical and chemical properties of cow's milk or of any other. An artificial cow's milk in



FIG. 46.

which oleomargarin has replaced the ordinary "butter" fat is shown in Figure 45.

This general procedure may be varied, of course, to suit different circumstances. One may begin with other proteins of milk instead of the casein, or with the whole set together which is found in the milk. Or other proteins may be used instead of the normal proteins of milk and so

mixtures physically identical with mammalian milks but of a different chemical composition may be produced. In place of the normal proteins of milk, we have in this way used the proteins of egg, of blood and of muscle. "Milks" produced with the proteins of the first two are shown in Figure 46. We have also used gelatin, and since the hydrophilic character of the colloid is the essentially important element, we have made "milks" of soap and of carbohydrates (dextrin). In place of butter-fat or oleomargarin, lard may be used, or other animal fats, or cottonseed oil including its hydrogenated derivatives.

From a physical point of view, there is no difficulty in replacing the animal or vegetable fats through mineral oils; and the salts or sugars that we may care to put into a milk offer wide realms of choice both as to character and concentration.

VIII. ON THE MIMICRY OF MUCOID
SECRETION.

VIII. ON THE MIMICRY OF MUCOID SECRETION.

THE following observations made in the course of our study of the formation and the breaking of emulsions have so much to do with a possible understanding of the ways and means by which the mucoid secretions are formed upon the mucous surfaces that a few paragraphs regarding them seem justified.

§1.

In the steady growth of the successful re-analysis of biological behavior in the terms of colloid chemistry, several of the phenomena associated with the formation of the mucoid secretions present difficulties. In the case of the essentially aqueous secretions like urine and sweat, it seems fairly well settled that they are not given off "as such" but are divisible into two phases: — the secretion of water and the secretion of dissolved substances.¹ The secretion of water is primary, while a leaching out by the water of the various dissolved substances found in the secreting cells follows secondarily. The combined process yields the completed secretion. But the dissolved substances in these instances are *crystalloid* in character; in other words, readily capable of passing into and through the colloid membrane which is constituted by the cells making up the secreting parenchyma. When certain *colloids* appear in the secretions, as when albumin appears in the urine, the problem may still remain relatively simple, for under the conditions which lead to albuminuria it is easily possible to discover agencies at work — such as the production or accumula-

¹ See MARTIN H. FISCHER: *Oedema and Nephritis*, 324 and 512. Second edition, New York, 1915. There references to the original studies may be found.

tion of acids, of urea, or of various amins — which render more diffusible the ordinarily non-diffusible proteins of the kidney. But this explanation proves inadequate when we come to secretions of the mucoid type.

Since the mucins are highly colloid, it is not only difficult to see how, through processes of diffusion alone, they get out of the cells in which they are formed into the secretions themselves, but the problem is further complicated by the fact that the mucoid secretions may be so thick — one needs but to think of the tenacious secretions of certain plants, or of the discharges from the respiratory passages or the alimentary tract in certain physiological and pathological conditions — that one cannot believe that the secretions ever came ready-made in so highly hydrated a form from the cells themselves.

In an attempt to explain the matter physico-chemically, it has been suggested¹ that in these mucoid secretions practically non-hydrated (unswollen) colloids are first pushed off by the mucous cells upon their surfaces, and that these swell subsequently when water becomes available, either through the secretion of water by the cells themselves, or from without.

§2.

In the following model much that is analogous to this idea of their formation and much that is applicable, in consequence, to the mechanism of the formation of these mucoid secretions both in plants and in animals, is not only to be observed directly, but since the observed phenomena are capable of analysis in the terms of physical and colloid chemistry, the possibility is tacitly suggested that the analogous biological phenomena may also some day be similarly analyzed.

To simulate the protoplasm of mucous cells, a mixture is made in a mortar of a small amount of powdered gum of

¹ MARTIN H. FISCHER: *Physiology of Alimentation*, 187, New York, 1907.

acacia in a cubic centimeter or two of cottonseed oil. Such a mixture after being thoroughly triturated appears under the microscope as a continuous oil layer in which the jagged particles of broken acacia are readily visible (Figure 47).

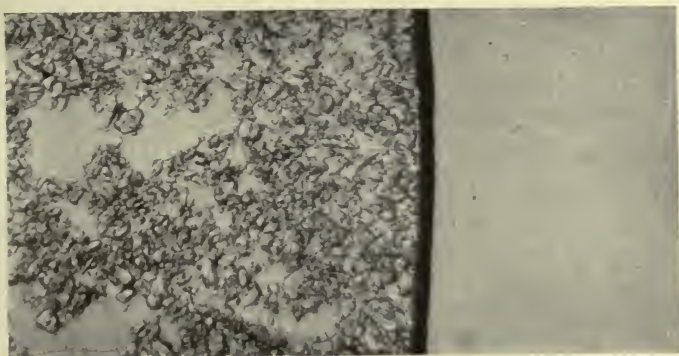


FIG. 47.

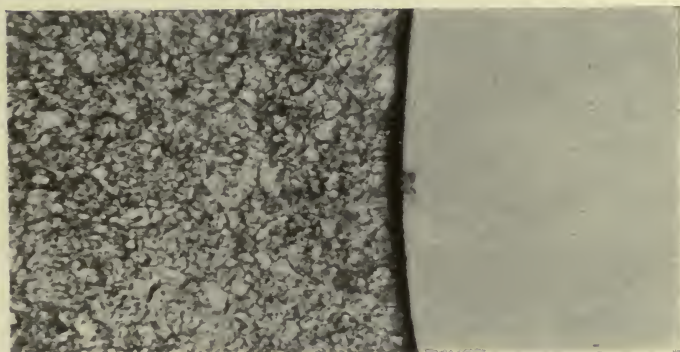


FIG. 48.

If now a drop of water is allowed to touch the edge of this oil layer, an interesting set of changes occurs. The oil edge is observed to show surface motions (surface tension movements) and the acacia particles within the oil mass are rapidly carried to the surface of the oil and extruded (Figure 48). Such extrusion is entirely analogous to the extrusion of foreign substances — such as ink particles, car-

mine particles, or other substances — by living cells. The particles of acacia as soon as extruded from the oil “dissolve” in the water covering the oil and in so doing, cover the oil with a tenacious, mucoid mass.

The “solution” of the acacia particles is not only readily observable microscopically but may be observed macroscopically in the rather rapid thickening of any water brought in contact with the acacia-oil mixture.

While the oil which contains the acacia particles may not be compared directly to protoplasm from a chemical point of view, it does in its “liquid” behavior act like it physically. Protoplasm, too, is best conceived of as a physical mixture of several mutually immiscible liquids.

§3.

The observations detailed here may perhaps serve not only for the demonstration in class of phenomena in “non-living” matter strikingly like those observable in living cells, but in so doing may suggest also the analysis of such “living” phenomena in the terms of surface tension, solubility, etc.

IX. ON THE MIMICRY OF SOME ANATOMICAL
STRUCTURES.

IX. ON THE MIMICRY OF SOME ANATOMICAL STRUCTURES.

I. INTRODUCTION.

§1.

THE history of anatomy may be divided into two parts: a morphological division and a physiological one. Under the former heading, description has been an end in itself; under the latter, this has been supplemented by an inquiry regarding *why* the structure has come to pass. The older gross morphological anatomy with its attendant gross physiology began to give way, in the middle of the last century, to a cellular anatomy and a cellular physiology, a development which culminated in that ultra-refinement of anatomical and physiological analysis of the last decade which describes the internal structures of cells themselves and of the protoplasm constituting them. Names inseparably connected with this newest but most important school of physiological anatomy are those of WALTHER FLEMMING,¹ O. BÜTSCHLI,² ALFRED FISCHER,³ W. B. HARDY⁴ and C. B. DAVENPORT.⁵

These paragraphs merely add to the studies of these observers, being of interest chiefly in that they show how from simple colloids and colloid mixtures exposed to slightly varying external conditions (as expressed, for example, in the removal or addition of water) complex morphological pictures result which are strikingly like those observed in the anatomical structures characteristic of living matter.

¹ WALTHER FLEMMING: *Zellsubstanz, Kern und Zelltheilung*, Leipzig, 1882.

² O. BÜTSCHLI: *Untersuchungen über Structuren*, Leipzig, 1898.

³ ALFRED FISCHER: *Fixirung, Färbung und Bau des Protoplasmas*, Jena, 1899.

⁴ W. B. HARDY: *Proc. Roy. Soc.*, **66**, 95 (1899); *Am. Jour. Physical Chem.*, **4**, 254 (1900); *Zeitschr. f. physik. Chem.*, **33**, 326 (1900).

⁵ C. B. DAVENPORT: *Experimental Morphology*, New York, 1908.

§2.

As generally recognized by the experimental morphologists, the problem of growth may be divided into two parts: a first, which may be regarded as *growth proper* and a second which is best discussed under the heading *differentiation*. The former is best defined as an increase in volume which, as we have previously pointed out,¹ is best conceived of as due to an increased swelling of the affected cell, tissue or organ undergoing growth. This increase in volume, which is generally looked upon as a "second stage" in growth, is secondary to a "first stage" which in its turn consists of a laying down of colloid materials, or of a change in conditions surrounding such as have been laid down which make these absorb an increased amount of water.

We have also emphasized how, through inequalities in the amount of water thus absorbed, stresses and strains are induced within the growing (swelling) colloid masses constituting the individual cells or organs, which lead to the production of curvatures in them, commonly known as growth curvatures and generally held to represent a response to certain chemical changes occurring within the protoplasm itself, or to such as are produced in the protoplasm through the various "tropisms" to which growing plants (SACHS) or animals (LOEB) may be subject.

But not only may growth proper — as well as certain inequalities in growth which we have thus far touched upon and which already bring with them the first elements of differentiation — be thus interpreted in the terms of colloid chemistry, but even those very complicated cellular changes which are more readily accepted under the term *differentiation* may be thus understood. Some years ago FISCHER and WOLFGANG OSTWALD² pointed out that so complicated

¹ MARTIN H. FISCHER: Pflüger's Arch., **124**, 70 (1908); *ibid.*, **125**, 99 (1908); (Edema and Nephritis, 372, 2nd Edition, New York, 1915.

² MARTIN H. FISCHER and WOLFGANG OSTWALD: Pflüger's Arch., **106**, 229 (1905).

an example of cell differentiation as astrophere formation may safely be defined as a localized and oriented gel formation.

§3.

In the course of these studies on emulsions, we were frequently struck by the complexity of the structures produced when emulsions are subjected to the simple process of drying, to increases in concentration of the one phase or the other, to the addition of water, the addition of various extraneous substances, etc.

These pages would present through photographs a few of the structures thus observed and state the conditions under which they were obtained. The similarity between them and certain histological pictures is so striking that one cannot avoid the conclusion that the nature of the forces producing each must be very similar; and since in the formation of even the most complex of the structures reproduced herewith, we know the forces concerned to be relatively simple in character and capable of analysis, it seems probable that the explanation of the mechanism by which similar forms observed in living matter are produced is likely to prove equally simple.

2. ON THE MIMICRY OF CERTAIN ANATOMICAL STRUCTURES.

§1.

It is fairly well settled and quite generally accepted that all of the three allegedly fundamental structures composing protoplasm itself — the granular, the fibrillar, the honeycomb — are merely expressions of inclusion or separation phenomena in a previously homogeneous phase. When, for example, in one optically homogeneous liquid phase, a second liquid is divided which has a different index of refraction, or when in a previously homogeneous liquid phase the second is made to appear which has a different index of refraction, a granular structure results.

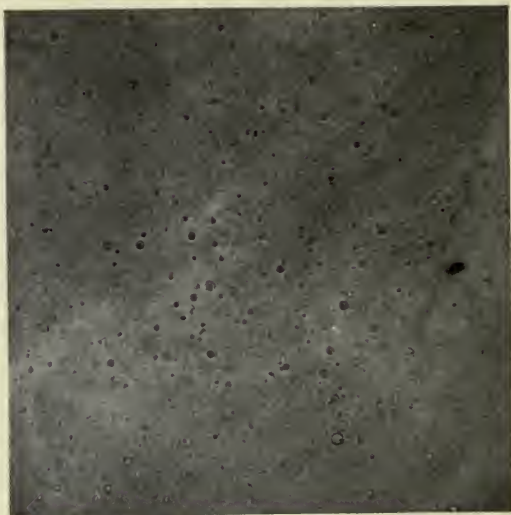


FIG. 49.

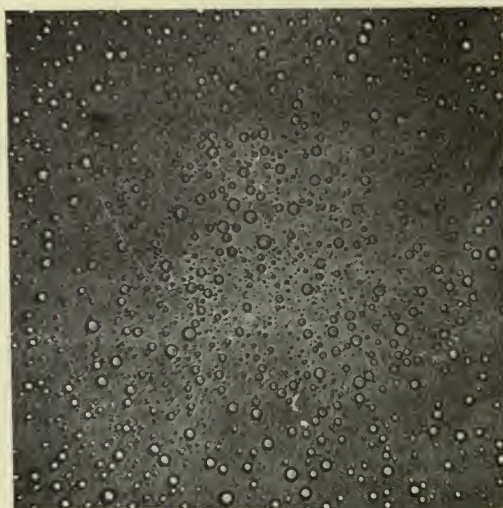


FIG. 50.

This phenomenon is readily observable in optically homogeneous soap solutions (like 25 percent potassium soap in water) when a very dilute acid (like the fumes of the laboratory or a $\frac{1}{100}$ normal acid of any sort) is permitted to diffuse into them. When this occurs, the previously clear soap (because of a separation of the insoluble fatty acid) becomes opalescent or milky and, on examination under the highest powers of the microscope, is seen to teem with

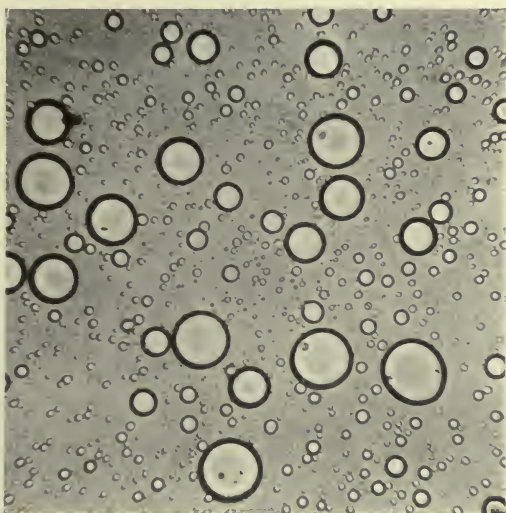


FIG. 51.

minute refractile bodies in active Brownian movement, as shown in Figure 49. From this originally highly dispersed granular structure there evolves a coarser one, as shown in Figure 50, if the acid-treated soap is left to itself for a time; and in the course of some hours or days, such a coarse emulsion of fatty acid in salt water as is shown in Figure 51 results.

If the experiment is carried on macroscopically, a continuous layer of fatty acid is likely to accumulate above the aqueous phase.

When such separation of fatty acid from soap is car-

ried out under conditions which do not destroy the hydrophilic nature of the liquid medium surrounding the fatty acid droplets; the minute fatty acid granules remain in finely divided form. This can be accomplished, for ex-

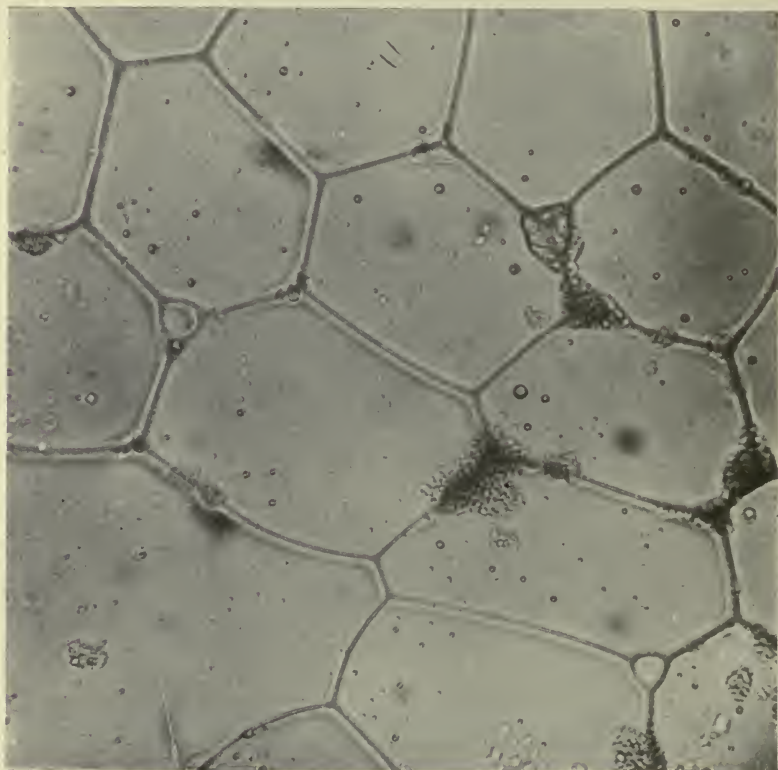


FIG. 52.

ample, by mixing the original soap solution with gelatin, when a more lasting picture of the type shown in Figure 49 is obtained.

§2.

When the separation of one liquid phase in a second, as that of fatty acid in an aqueous dispersion medium, is permitted to occur in solutions of proper composition and con-

centration (hydrated colloids of high concentration, like concentrated soaps), the separating phase may yield enough non-coalescing globules to make up most of the field. This

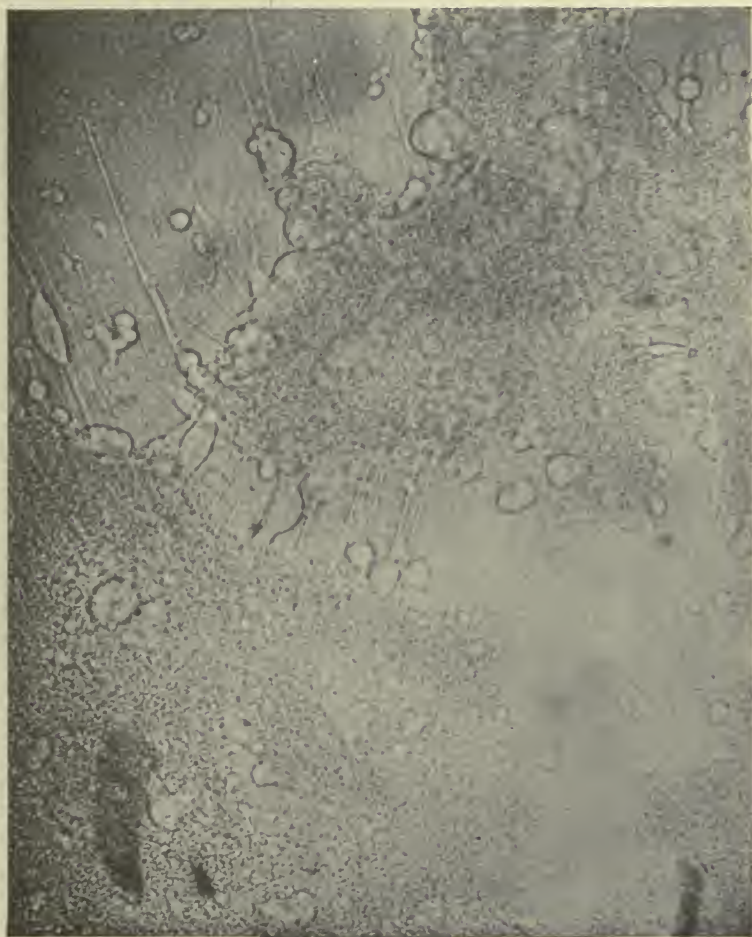


FIG. 53.

picture is produced when concentrated soaps are treated with acid. It may also be produced when a gas, like air, is beaten into a soap solution to make a foam. Under such circumstances, mutual pressures result which deform the originally spherical globules of fatty acid or air and such

honeycomb structures form as are illustrated in Figure 52. Such structures, which have been brilliantly described by BÜTSCHLI, remind one not only of the fundamental honey-

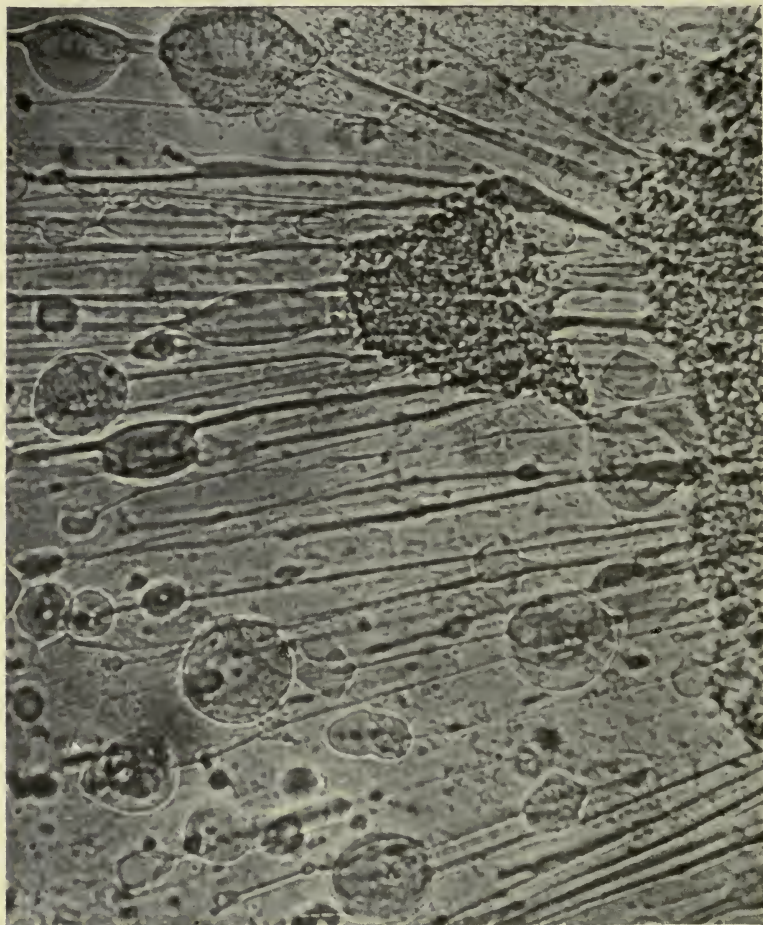


FIG. 54.

comb structure observed in protoplasm itself, but of those coarser honeycomb structures which may be observed in the alveolar structure of the organs of various mammals. Figure 52, for example, looks not unlike a microscopic section of lung.

§3.

In Figure 53 is shown the microscopic appearance produced in the drying of an oil-in-soap (25 percent potassium soap) emulsion. Of interest here are the "protoplasmic bridges" (of soap) formed between the shrinking fragments of emulsion. These bridges are not unlike those seen histologically in materials derived from living sources. When very fine, these bridges are not unlike the bridges observed between the epithelial cells (prickle cells) of the skin. In coarser form, especially when globules of oil become enmeshed in them, they remind one of the rods and cones of the retina, as illustrated in Figure 54.

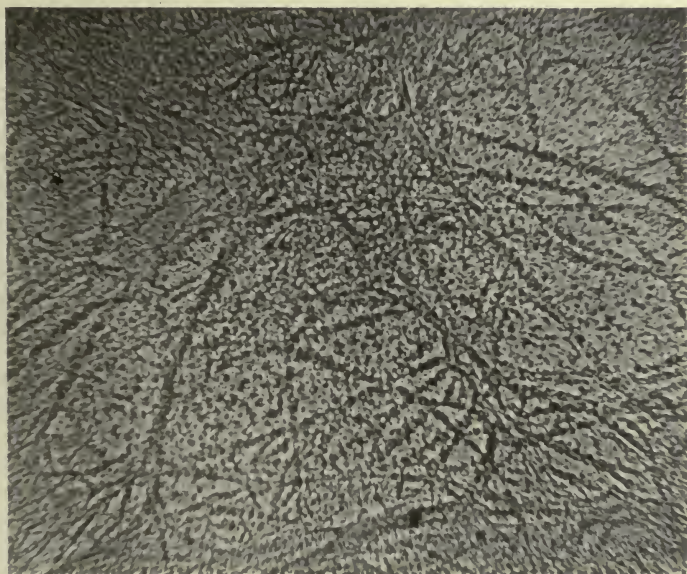


FIG. 55.

§4.

A protoplasmic structure combining the fibrillar and granular is shown in Figure 55. A fibrillar structure composed of granules arranged in threads is often referred to



FIG. 56.

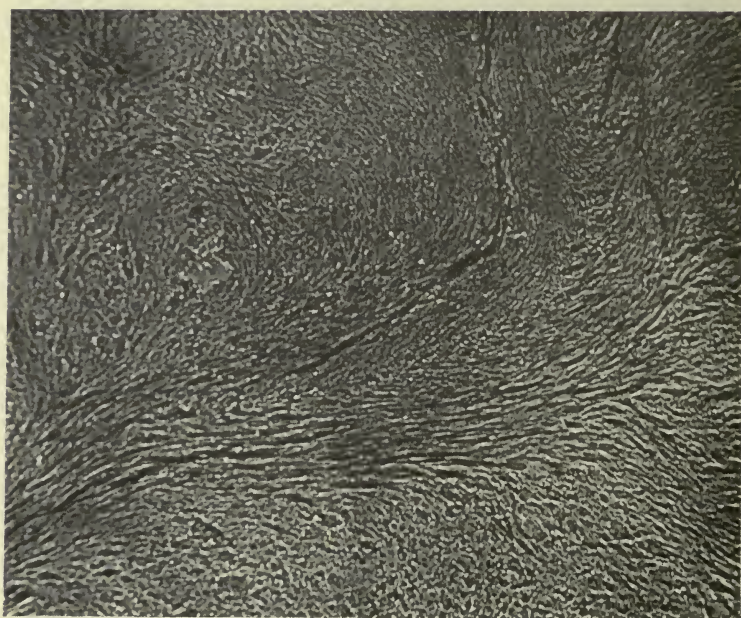


FIG. 57.

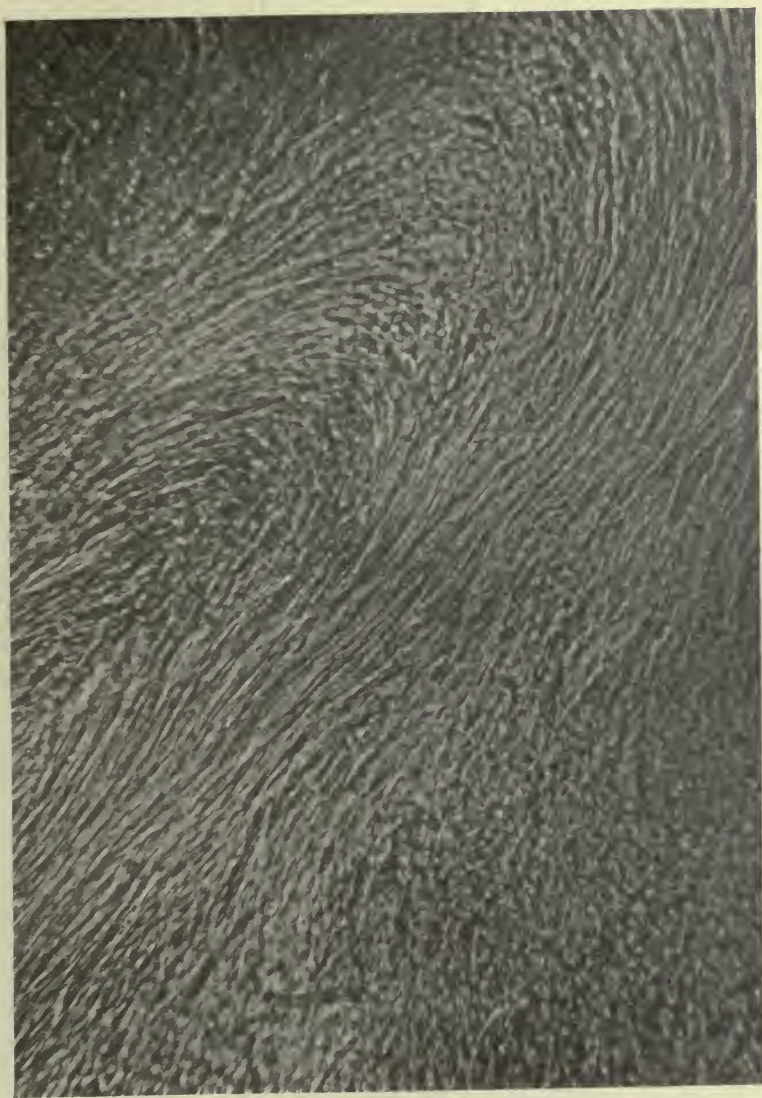


FIG. 58.

in the text-books of histology. The original matrix for Figure 55 is a partially swollen mixture of acacia and dried egg-white. When a little dilute acid is allowed to diffuse into a drop of this material under a cover slip, the originally fairly homogeneous mixture not only begins to swell but some of the proteins (the globulins) of the egg-white are precipitated as tiny granules. These tend to accumulate in the acacia threads which are being dragged through the swelling mass and so the appearance of such granular threads as are shown in Figure 55 comes about.

§5.

When a mixture of two partially hydrated colloids (just such mixtures as are formed in those parts of plants and animals which are in the so-called first stage of growth) like acacia and egg albumin is permitted to swell further through the addition of a little water, stresses and strains occur in the swelling mixture, owing to the differences in the indices of swelling of the two colloids, which yield interesting morphological results. (Such increased imbibition of water corresponds, as is well known, to the second stage of growth.) The edge of such a swelling mass is shown in Figure 56. The projections forming at the free surface of the mixture remind one strongly of the nodules which mark the first evidences of the formation of new organs in embryos, of the mucous membrane tufts (villi) of the intestine, etc.

§6.

But the deeper portions of such a picture as is shown in Figure 56 are also of interest. The stresses and strains incident to the unequal swelling of the acacia and the protein yield interesting structures here also. As Figure 57 shows, structures that remind one strongly of embryonic connective tissue, of rapidly growing involuntary muscle cells, of the appearance of fibromas, myomas and sarcomas,

etc., are produced. Even when highly magnified (850 diameters), as shown in Figure 58, this appearance is not destroyed.

§7.

The fine markings which we observe in our skins (in their purest form, in those portions which are distant from joints and not subject to direct creasing) seem also to be but the expression of the effects of drying in hydrated colloids. Structures similar to these skin figures may be observed in drying proteins like egg-white as first described by O. BÜTSCHLI.¹ When thin layers of egg albumin are spread upon a glass slide and left to dry in the air, linear crackings occur as shown in Figures 59 and 60. These linear cleavages remind one not only of the linear crackings observable in our own skins but in many other drying animal and plant tissues. Under higher magnifications of the microscope they present the appearance seen in Figure 61.

It is only necessary to increase the thickness of the drying egg white film to have these essentially linear crackings give rise to more complicated structures such as are shown in Figure 62. In addition to the linear crackings, there now occur large numbers of transverse ones which yield polygons of various sizes and shapes. But in addition to the formation of these polygons, secondary inspissation figures of great beauty begin to appear within many of them. While observable in Figure 62, they are more clearly demonstrated at somewhat higher magnification, as shown in Figure 63 or in Figure 64 which is magnified 850 diameters.

All these linear, polygonal and circular inspissation figures may be seen in the normal skin, but the last of them reminds one most definitely, perhaps, of figures observable macroscopically or microscopically in certain skin diseases which are associated with a thickening of the epithelial structures and their abnormal drying. The circular inspissation

¹ O. BÜTSCHLI: Untersuchungen über Strukturen, 34, Leipzig, 1898.



FIG. 59.

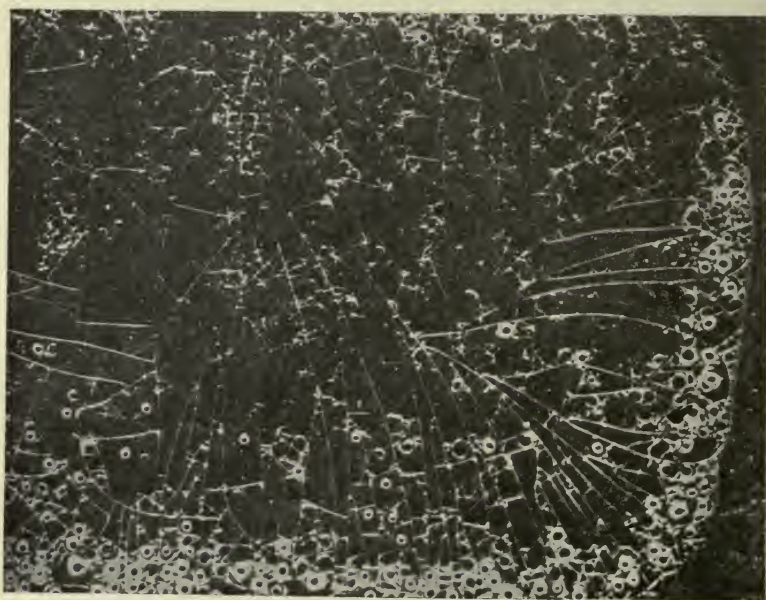


FIG. 60.



FIG. 61.

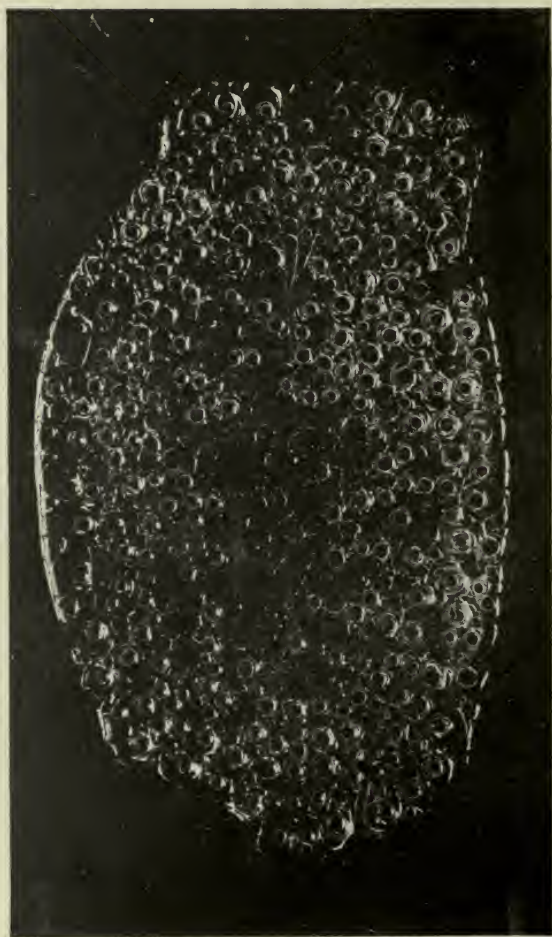


FIG. 62.

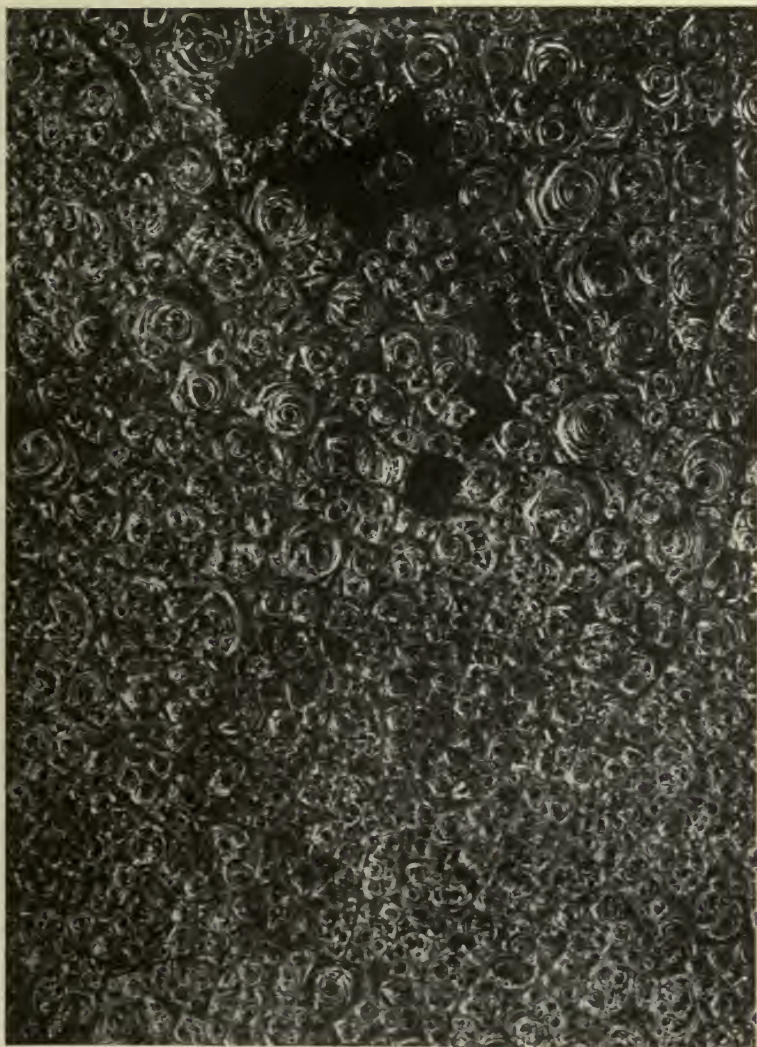


FIG. 63.

sation figures also bring to mind the appearances characteristic of certain cancers (epitheliomas) when these are studded with "whorls" or "pearls."



FIG. 64.

3. ON THE PROTECTIVE COVERINGS OF PLANTS.

In concluding these descriptions of microscopic and macroscopic structures as produced in the processes of hydration and dehydration of individual and mixed hydrated colloids, we should like to draw attention to a finding previously commented upon.¹ As emphasized there, an oil-in-hydrated protein emulsion tends on simple drying to

¹ See page 52.

pass over into a hydrated protein-in-oil type. The process may be observed, for example, in the drying surface of ordinary egg yolk. The beads of oil which form upon the surface are shown in the field *b* of Figure 65. As the oil droplets increase in number they tend to coalesce and to form a continuous film. If the oil is of a drying type, a continuous oil film forms over the surface of the emulsion. Such a continuous oil film is shown in the field *a* of Figure 65. We emphasize these changes and the appearances thus

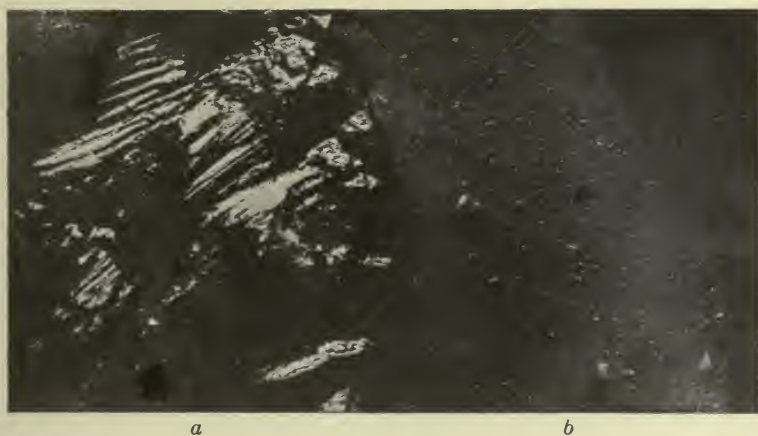


FIG. 65.

produced because we believe they explain not only the mechanism but also the appearance characteristic of similar structures seen in flowers, leaves, fruits, etc. Not only are the surfaces of many flowers, for instance, studded with minute oil droplets, but in many flowers and, still better, in many leaves and fruits, such droplets may be observed to coalesce (with subsequent drying of the oil) to form the shiny, continuous oil films covering these structures.¹

¹ If, as the conversion of the oil-in-water emulsion to the water-in-oil type occurs upon the surface of a fruit, for example, there remains behind on the surface of the oil film a drying protein, silicate or other material, then the fruit becomes covered with a "bloom."

The importance of these waterproof films (in the case of leaves, for example) is self-apparent. Were plants not possessed of them, every rain would destroy them. The water-in-oil type of emulsion protects the plant against the effects of rain from without; the oil-in-water type within the plant allows it to imbibe this same water from the soil after the rain has fallen.

X. CONCLUDING PARAGRAPHS.

X. CONCLUDING PARAGRAPHS.

§1.

IF, in retrospect, we try to state the value of the preceding pages, we may say that they represent an attempt to analyze colloid-chemically the third phase in the reaction of living matter to injury. We did not anticipate such a finding when we began our studies, but this conclusion is nevertheless forced upon us.

The one *universal* element in that reaction of living matter to injury, which is called inflammation, is a swelling of the injured part. This is also the *first* phase in the reaction. In the terms of colloid chemistry, we have defined this swelling as an increased hydration capacity of the tissue colloids. If the conditions causing the inflammatory reaction are sufficiently severe and sufficiently lasting, a "clouding" of the swollen tissues takes place, the two together yielding "cloudy swelling." This clouding we have defined as a dehydration with consequent precipitation of a second group of the tissue colloids within the mass of the previously discussed swelling ones. Accompanying this *second* stage in inflammation or following it comes that *third* stage with which these pages have chiefly dealt, namely that of "fatty degeneration."

When we parallel these three stages with the altered *function* which accompanies the "inflammatory" reaction to injury, we note that even the first stage may be accompanied by much disturbance, that the second may show this in extreme form and that the third may show a complete loss of the characteristic functions of the involved tissues. We emphasize these facts because the orthodox pathologists pass rather lightly over these first morphological evidences of injury which in their terms are mere "albu-

minous" and "fatty degenerations." And yet if it is but remembered that function and not morphological pathology is the matter of real interest to the worker in medicine and biology, it will at once be seen that all the changes in living tissues beyond these first and largely ignored ones are of a type of more interest in the dead house than to the still living host that harbors them.

The reasons for these obvious conclusions exist in the possibilities and non-possibilities for the *reversal* of the process in these three states. The changes incident to the mere swelling of the first stage are still quite readily reversible; even those of the second or clouding stage are still largely reversible, but more slowly. The fatty changes characteristic of the third mark the transition point to the final or *fourth* and irreversible stage of necrosis (the stage of the irreversible precipitation or "coagulation" of the protein colloids of the affected tissues).

While a cell which has suffered a "fatty degeneration" may still recover, it is scarcely able to do this through mere reversal of the conditions which have brought about the pathological state. Under the conditions prevailing within our bodies, for example, many of the changes characteristic of fatty degeneration are already on the edge of the irreversible and so mark the dividing line between the living and the dead. Even when the normally very finely divided oil droplets of our cells have coalesced into the larger, more readily visible ones of "fatty degeneration," the fat has already passed into a state in which, on reversal of the conditions which made for the degeneration, it will not go back into the finely divided form. But if the state of the fat is not of fundamental importance for the continuance of the living state of the cell and if those changes (the cloudy swelling) within the cell which affect the proteins, for example, are still reversible, the cell as a whole may go on living. Complete restitution to the normal, however, can only be effected by indirect means. There is no machine which in our bodies, as in our laboratories, will sub-

divide again the fat; but nature can, by digestion of the fat to fatty acid and glycerin and their redeposition as fat in the normal finely divided form, bring about the original state of the cell. In this way the first stages of "fatty degeneration" still remain of an ultimately reversible type. But except as such digestion with redeposition of the fat is still possible, even the mere coalescence of the small fat droplets into the larger ones represents in our bodies a practically irreversible physical change. And once this coalition of the fat droplets has gone to the point of gross separation (accompanied by the great dehydration and precipitation of the cell proteins with its accompanying separation of water which we call "tissue softening") the process is absolutely irreversible and the death of the part (necrosis) is at hand. In our laboratories we can again rebuild our original system, but in a brain, in a cut nerve, or in a parenchymatous organ this is out of the realm of the possible. Nature can repair the defect only as she builds new tissues into the stricken area.

§2.

We have frequently been asked what is the bearing of these pages upon the practical problems of chemistry, of biology and of medicine.

It need not be emphasized that they replace with definite laws much of what was empirical in the production, maintenance and destruction of the emulsions as these appear to the pharmaceutical chemist, the purveyor of food, the dairyman, or the manufacturer of rubber, lubricating materials, or soap products.

To those biologists and physicians whose daily endeavors are not tinged with imagination or contaminated by philosophy, these pages may well be admitted to be of no practical worth whatsoever. To the others, they have a limited value. It is the fundamental duty of the physician to determine how many of the changes which he sees in the

ill before him are of a reversible type and how many are irreversible. Only as the observed changes are completely reversible is "cure" possible. The eternal debate of the value of therapeutic procedures seems never to end. Why need the fact be argued that any "disease" treated by any therapeutic scheme whatsoever might have "gotten well anyway"? This only states that the series of changes from which the patient suffered were still of a reversible type. But only changes of this type, and no others, are curable. The important function of the physician is to recognize the fact, and then, instead of leaving the job to nature and chance, aid as far as possible in establishing the reversal.

In the stages of swelling and of albuminous degeneration we are already far into the territory of altered function; but, as we have previously emphasized, a proper recognition of the nature of the changes before us gives many practical hints both as to prevention and as to aid toward reversal of these changes. In the problem of the changes in fat distribution within cells as discussed in these pages we come to the dividing of the ways. There still remains a certain margin wherein we may assist nature in bringing about reversal. On the other hand, there has arrived a dangerous proximity to the line of the irreversible. For the latter, medicine offers, in the established case, only the expedient of trying to make the irreparable more tolerable. But such a better understanding of our biological mechanisms still brings this with it. If it does not teach us how to repair trouble, it at least emphasizes the importance — if the owners will permit it — of advice destined to keep our biological mechanisms out of such trouble. And that seems to be the heart of what may be termed the new medicine.

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